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(54) Title: COFORMULATION METHODS AND THEIR PRODUCTS
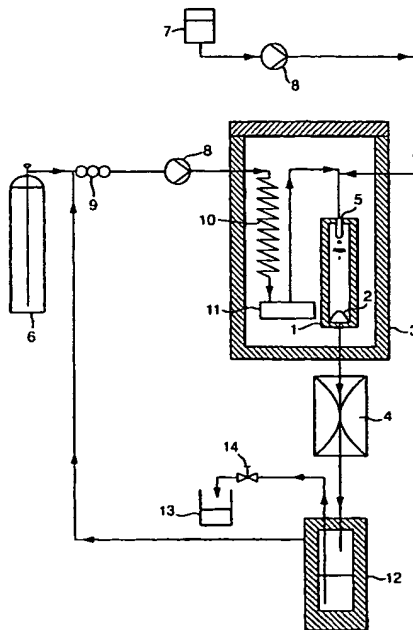
(57) Abstract: A coformulation of an active (preferably pharmaceutically active, for instance a COX-2 enzyme inhibitor) substance and an oligomeric or polymeric excipient, containing at least 10 % of the active, between 80 and 100 % of which is amorphous. The amorphous phase is stable, with respect to the crystalline phase(s), for at least three months after its preparation when stored at between O and 10 °C. The invention also provides processes, preferably involving SEDS™ particle formation, for preparing such a coformulation.

Coformulation Methods and their Products

This invention relates to methods for coformulating an active substance and an oligomeric or polymeric excipient. It also relates to the particulate products of such
5   methods.

In particular, it relates to new applications and products of the particle formation technique known as SEDS™ (Solution Enhanced Dispersion by Supercritical fluids), which is described in WO-95/01221 and (in modified versions) in WO-96/00610, WO-98/36825, WO-99/44733 and WO-99/59710. It has been found that this technique may
10   be used to produce novel coformulation products, especially of pharmaceutically active ingredients with oligomer or polymer excipients, having advantageous physicochemical characteristics.

It is known to coformulate pharmaceuticals with polymers in order to modify their solubility profiles and hence, for example, improve the dissolution of an otherwise
15   poorly soluble drug, or slow the dissolution of a highly soluble drug so as to control its release after administration or to reduce its toxicity.

Known techniques for preparing such drug/polymer coformulations include solvent evaporation and coprecipitation, from a mixture of the drug and polymer in a common solvent system. Such approaches are often limited however by manufacturing
20   difficulties, including environmental constraints, solvent problems such as the need for multiple solvent systems and the consequent risk of phase separation, harvesting difficulties and the high levels of polymer often required. Other major limitations tend to be the poor physical properties and processing characteristics of the particulate products, which can be cohesive and difficult to handle, may contain unacceptable levels of residual
25   solvent or non-uniform drug distributions, may suffer poor chemical and physical stability and are often large particles which need to be further reduced in size before they can be processed into commercial products. It can also be difficult to control the morphology of the drug in the system, ie, the relative proportions of its crystalline and (more soluble, and hence generally preferred) amorphous phases.

30   There is a tendency too for amorphous phase drugs, even in the presence of polymeric excipients, to be meta-stable with respect to the crystalline phase. Over extended storage periods an amorphous drug can revert to its crystalline form, with

consequent changes in its dissolution profile. The degree of instability may depend on storage temperature (in particular with respect to the glass transition temperature, Tg, of the amorphous solid) and humidity, and on relative drug and excipient concentrations. It can also be affected to some degree by the choice of excipient, and even by the manner in which the drug/polymer mixture was prepared. (See references [1] – [5].)

An active substance such as a drug should have stable characteristics under "normal" storage conditions, typically at room temperature and for shelf lives of at least two years. Thus for pharmaceuticals, standards are being developed which require stability for reasonable periods at 25°C. Previous attempts to coformulate drugs with excipients have generally failed to achieve an amorphous phase active with such a high level of stability; in many cases recrystallisation has been observed within days, if not hours ([1] – [5], supra).

Matsumoto and Zografi [6] claim more recently to have stabilised the amorphous phase of the drug indomethacin, using poly vinyl pyrrolidone (PVP) as an excipient. They report storage periods of up to 20 weeks at 30°C without recrystallisation, for coformulations containing up to 95% indomethacin. The properties of the system are explained in terms of hydrogen bonding between the drug and polymer, which disrupts the drug dimers associated with the crystalline phase.

The products of the present invention are coformulations of an active substance, typically a pharmaceutically active substance, with an oligomeric or polymeric material. They contain significant amounts of the active substance in its amorphous form, the stability of which can be much greater than in analogous prior art coformulations. They can be used in particular in the design and manufacture of drug delivery systems, to control drug release and/or enhance bioavailability.

According to a first aspect of the present invention, there is provided a coformulation of an active (preferably a pharmaceutically active) substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, wherein the amorphous phase active substance is stable, with respect to its crystalline form(s), for at least three months after its preparation when stored at between 0 and 10°C, conveniently 6°C. It is preferably also stable, for the same period, when stored at 25°C.

By "stable" is meant that, over the specified time period, there is no significant change in the X-ray diffraction (XRD) pattern of the coformulation and, where appropriate (ie, where measurable) in its differential scanning calorimetry (DSC) profile. There is preferably no significant change in the dissolution profile of the coformulated

5   active substance. In other words, there is little or no detectable change in the amount of any crystalline form(s) present after the specified time period, preferably less than 10%, more preferably less than 1%, most preferably less than 0.1% change with respect to the initial amount. Yet more preferably, the coformulation contains no detectable crystalline active substance both pre- and post-storage.

10   For the purpose of assessing stability, the coformulation may need to be stored in a protective atmosphere if it is particularly sensitive to humidity. Low humidity levels, preferably a moisture-free environment or at least between 0 and 5% relative humidity (RH), may be achieved in conventional ways, for instance by storing in moisture resistant packaging or in a desiccator.

15   The amorphous phase active substance is preferably stable for at least six, more preferably nine or twelve months after its preparation, and is most preferably stable for at least eighteen, twenty four or thirty six months after its preparation.

It is preferably also stable, for the periods mentioned above, when stored at 25°C and up to 60% RH. Even more preferably, it is stable when stored at 40°C, most

20   preferably at 40°C and up to 75% RH.

A coformulation according to the invention is typically an intimate mixture of the active substance dispersed in a "matrix" of the oligomer or polymer excipient, in which the solubility characteristics of the active substance are modified due to the presence of the excipient. Usually the dissolution rate of the active substance will be enhanced by

25   coformulating it, but in some cases (for instance of use in "controlled release" drug formulations) it may be inhibited.

The products of the present invention, when made by a SEDS™ process, tend not only to be more stable but also generally less cohesive, more free flowing (having discrete particles) and easier to handle and process, than analogous coformulations made

30   according to more conventional methods (in particular prior art coformulations containing amorphous or even semi-crystalline actives, which can have extremely poor

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handling properties). The products of the invention can also be made with particle sizes down to between 0.1 and 1 μm, with relatively narrow size distributions.

Another advantage of the products of the present invention is that they can generally be prepared in the absence of additional surfactants, which many prior art coformulations require as stabilisers. They also usually contain significantly reduced levels of residual solvents. Moreover, since they are precipitated rapidly from homogeneous active/excipient solutions, they tend to contain more uniform active distributions, a characteristic which is especially important when formulating low dosage drugs.

The coformulations of the invention are preferably prepared by a SEDS™ process, from one or more "target solutions" containing the active substance and/or the oligomeric or polymeric material. It has been found that SEDS™-coformulated products can contain higher levels of amorphous phase active than is often possible using prior art production methods, and more significantly that the amorphous phase is more stable, with respect to reversion to the crystalline phase, than in conventionally produced coformulations. This may be due to increased intimacy of the active substance/excipient mix, and/or to reduced levels of residual solvent, although we do not wish to be bound by these theories. It may also be the case that the SEDS™ method involves such rapid particle formation that neither the drug nor the excipient molecules are able to group themselves with any degree of order as they precipitate. The slower prior art coformulation processes, such as solvent evaporation and spray drying, may result in the formation of "microdomains", small seed crystals that can act as nucleation sites for subsequent re-crystallisation. If a coformulation contains a significant number of such nucleation "seeds", it will almost inevitably revert to the crystalline form on storage, often within a short period.

That SEDS™ may be used to prepare such coformulations is surprising in view of earlier literature on the process. In WO-95/01221, for example, there are examples of drug/polymer coformulations (salmeterol xinafoate and hydroxypropyl cellulose), but although these apparently demonstrate "disturbance" of crystallinity, it is clear from the appended DSC/XRD data that significant amounts of the crystalline drug are still present. Elsewhere in WO-95/01221 and WO-96/00610, there is emphasis on the ability of SEDS™ to yield crystalline materials, and most of the examples in those documents and

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in WO-98/36825, WO-99/44733 and WO-99/59710 show highly crystalline products when SEDS™ is used to process organic materials.

Thus, although SEDS™ is a fast precipitation process, which might otherwise have been expected to produce amorphous solids, in fact it has been shown to force the majority of organic compounds into a crystalline state. The addition of a polymer might be expected, as in Examples 10 and 16 of WO-95/01221, to reduce crystallinity levels, but it would not be predicted to achieve 100% amorphous drug systems, particularly at the relatively high drug loadings now found to be possible (in the past, high levels of polymer (80% or greater) tend to have been needed to give any significant reduction in crystallinity [2]). Moreover, the products of the invention have significantly improved long term stability (with respect to active re-crystallisation), which could not have been predicted from the prior art.

By "a SEDS™ process" is meant a particle formation technique as described in WO-95/01221, WO-96/00610, WO-98/36825, WO-99/44733 and/or WO-99/59710, in which a supercritical or near-critical (preferably supercritical) fluid anti-solvent is used simultaneously both to disperse, and to extract a fluid vehicle from, a solution or suspension of a target substance. Such a technique can provide better, and more consistent, control over the physicochemical properties of the product (particle size and size distribution, particle morphology, etc.) than has proved possible for coformulations in the past.

SEDS™ is also a one-step process; it can be used to precipitate both the active substance and the excipient at the same time, either from the same or from separate "target" solutions or suspensions, the target solution(s)/suspension(s) being co-introduced into a particle formation vessel with the anti-solvent, preferably through a coaxial nozzle with an appropriate number of concentric passages.

Other advantages of the SEDS™ process are described in prior art such as WO-95/01221, for example the ability to process sensitive active substances in a light-free and/or oxygen-free environment.

The anti-solvent used in the SEDS™ process is preferably supercritical carbon dioxide, although others (eg, as mentioned in the earlier SEDS™ literature) may be used instead or in addition.

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The oligomeric (which includes dimeric) or polymeric material may be any suitable excipient for the active substance, of whatever molecular weight and whether hydrophilic - such as a polyethylene glycol, hydroxypropyl methyl cellulose (HPMC) or polyvinyl pyrrolidone (PVP) - or hydrophobic - such as an ethyl cellulose (EC). It may be a biodegradable oligomer or polymer such as a polylactide or glycolide or a polylactide/glycolide. It may be crystalline, semi-crystalline or amorphous. It may be a homo- or co-oligomer/polymer, synthetic or naturally occurring.

Examples, of oligomeric or polymeric materials suitable in particular for coformulation with pharmaceutically active substances, include but are not limited to:

a)   traditional "natural" source materials, their derivatives and their synthetic analogues, such as acacia, tragacanth, alginates (for instance calcium alginate), alginic acid, starch, agar, carrageenan, xanthan gum, chitosan, gelatin, guar gum, pectin, amylase or lecithin.

b)   celluloses and cellulose derivatives, such as alkyl (for instance methyl or ethyl) cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose, microcrystalline cellulose or microfine cellulose.

c)   homo- and co-polymers of hydroxy acids such as lactic and glycolic acids.

d)   acrylates and their derivatives, such as the "Eudragit"™ polymers, methacrylic acids, or methacrylates such as methyl methacrylate.

e)   hydrated silicas, such as bentonite or magnesium aluminium silicate.

f)   vinyl polymers, such as polyvinyl chloride, polyvinyl alcohols, polyvinyl acetates, polyvinyl pyrrolidones, cross-linked polyvinyl pyrrolidones or carboxy vinyl copolymers.

g)   polymeric surfactants, such as polyoxyethylene or polyoxypropylene, or polyalkylene oxides such as polyethylene oxides.

h)   phospholipids, such as DMPC (dimyristoyl phosphatidyl choline), DMPG (dimyristoyl phosphatidyl glycerol) or DSPC (distearyl phosphatidyl choline).

i)   carbohydrates, such as lactose, dextrans, cyclodextrins or cyclodextrin derivatives.

j)   dendrimeric polymers, such as those based on 3,5 hydroxy benzyl alcohol.

k)   poly(ϵ-caprolactones), DL-lactide-co-caprolactones and their derivatives.

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l)   poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers,
     including block copolymers, such as are described in US-5,968,543 and US-
     5,939,453, also derivatives of such polymers, also such polymers with
     incorporated esters of short chain α-hydroxy acids or glycolic-co-lactic acid
5   copolymers.

Other suitable oligomers/polymers are listed in the literature on drug delivery
systems, for example the report by Brocchini in World Markets Series "Business
Briefing", Drug Delivery Supplement [7].

The oligomeric or polymeric material is preferably either a cellulosic material
10 such as EC, HPC or HPMC (including cellulose derivatives), a vinyl polymer such as a
polyvinyl pyrrolidone, a polyoxyalkylene (eg, polyoxyethylene or polyoxypropylene)
polymer or copolymer or a polylactide or glycolide (including lactide/glycolide
copolymers).

The active substance may be a single active substance or a mixture of two or
15 more active substances. It may be monomeric or polymeric, organic (including
organometallic) or inorganic, hydrophilic or hydrophobic. It may be a small molecule, for
instance a synthetic drug like paracetamol, or a larger molecule such as a (poly)peptide,
an enzyme, an antigen or other biological material. It preferably comprises a
pharmaceutically active substance, although many other active substances, whatever their
20 intended function (for instance, herbicides, pesticides, foodstuffs, nutriceuticals, etc.),
may be coformulated with oligomers or polymers in accordance with the invention. In
particular the active substance may be a material having low aqueous solubility, for which
coformulation with an oligomeric or polymeric excipient can increase the aqueous
dissolution rate and hence facilitate delivery.

25 In particular, it has surprisingly been found that SEDS™ may be used to
coformulate an active substance with an oligomer or polymer even when their respective
hydrophilicities are significantly different. Such pairings might previously have been
thought incompatible for coformulation. Examples include coformulations of relatively
polar actives such as paracetamol, theophylline or ascorbic acid with hydrophobic
30 polymers such as ethyl cellulose.

For some active substances, SEDS™ enables the preparation of coformulations
containing higher amorphous phase active loadings than has previously been possible.

Thus, a second aspect of the present invention provides a coformulation of (i) an active substance selected from the group consisting of paracetamol, ketoprofen, indomethacin, carbamazepine, theophylline and ascorbic acid and (ii) an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an

5 amorphous as opposed to crystalline form, and in which the active substance represents at least 10% of the coformulation, provided that if the active substance is indomethacin or theophylline, the oligomeric or polymeric material is not polyvinyl pyrrolidone.

In a coformulation according to the invention, preferably between 80 and 100%, more preferably between 90 and 100% or between 95 and 100%, most preferably 100%,

10 of the active substance is present in an amorphous as opposed to crystalline form. The active substance preferably represents at least 1%, more preferably at least 2% or 5% or 10% or 20% or 25% or 30% or 35% or 40% or 50% or 60% or 70% or 80% or 90% of the system. In other words, products according to the invention can contain high loadings of the active substance, of which all or substantially all is present as a single

15 amorphous phase.

Percentage concentrations are weight for weight unless otherwise stated.

Where the active substance is indomethacin and the excipient is ethyl cellulose (EC), preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25%

20 or 30% or 35%, of the coformulation.

Where the active substance is indomethacin and the excipient is hydroxypropyl methyl cellulose (HPMC), preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 10%, more preferably at least 20% or 25% or 30% or 35% or 40%, of the coformulation.

25 Where the active substance is indomethacin and the excipient is polyvinyl pyrollidone (PVP), preferably between 95 and 100% of the indomethacin is present in an amorphous form, and the indomethacin represents at least 20%, more preferably at least 25% or 30% or 40% or 50% or 60% or 65% or 70%, of the coformulation.

Where the active substance is carbamazepine and the excipient is EC, preferably

30 between 95 and 100% of the carbamazepine is present in an amorphous form, and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

Where the active substance is carbamazepine and the excipient is HPMC, preferably between 95 and 100% of the carbamazepine is present in an amorphous form, and the carbamazepine represents at least 10%, more preferably at least 20% or 25% or 30%, of the coformulation.

Where the active substance is theophylline and the excipient is EC, preferably between 95 and 100% of the theophylline is present in an amorphous form, and the theophylline represents at least 10%, more preferably at least 20% or 25% or 28% or 30%, of the coformulation.

Where the active substance is theophylline and the excipient is HPMC, preferably between 95 and 100% of the theophylline is present in an amorphous form, and the theophylline represents at least 1%, more preferably at least 2% or 5% or 8% or 10%, of the coformulation.

Where the active substance is ascorbic acid and the excipient is EC, preferably between 95 and 100% of the ascorbic acid is present in an amorphous form, and the ascorbic acid represents at least 1%, more preferably at least 2% or 5% or 8% or 10% or 15%, of the coformulation..

Where the active substance is ascorbic acid and the excipient is HPMC, preferably between 95 and 100% of the ascorbic acid is present in an amorphous form, and the ascorbic acid represents at least 10%, more preferably at least 20% or 25% or 30% or 35% or 40%, of the coformulation.

Where the active substance is a compound of formula (I):

((Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulfonyl)methylene]-dihydrofuran-2-one) and

the excipient is hydroxypropyl cellulose (HPC), preferably between 95 and 100% of the

Compound (I) is present in an amorphous form, and the Compound (I) represents at least

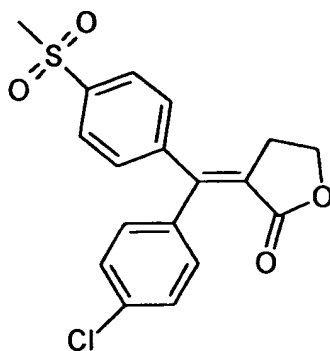5%, more preferably at least 10% or 15% or 20% or 21%, of the coformulation.

5   Where the active substance is a compound of formula (I) and the excipient is a

polyoxyalkylene polymer or copolymer, such as a polyoxypropylene-polyoxyethylene

copolymer, preferably between 95 and 100% of the Compound (I) is present in an

amorphous form, and the Compound (I) represents at least 5%, more preferably at least

10% or 15% or 20% or 24%, of the coformulation.

10   Where the active substance is a compound of formula (II):
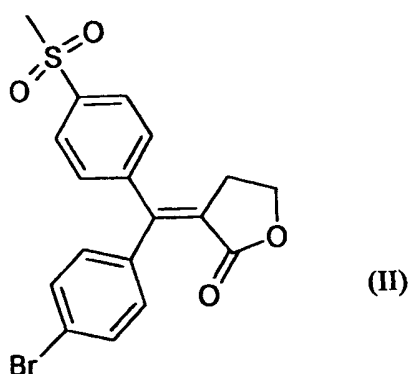
(II)

((Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one)

and the excipient is HPC, preferably between 95 and 100% of the Compound (II) is

present in an amorphous form, and the Compound (II) represents at least 5%, more

15   preferably at least 10% or 15% or 20% or 21%, of the coformulation.

In certain cases, SEDS™ can allow formation of the amorphous phase of active

substances which have (to our knowledge) previously only been prepared in their

crystalline phase(s). One example of this is the preparation of paracetamol/excipient

coformulations. A third aspect of the present invention therefore provides a

20   coformulation of paracetamol and an oligomeric or polymeric material, in which between

80 and 100% of the paracetamol is present in an amorphous as opposed to crystalline

form, and in which the paracetamol represents at least 1% of the coformulation.

In such paracetamol coformulations, preferably between 90 and 100%, more

preferably between 95 and 100%, most preferably 100%, of the paracetamol is present in

its amorphous form. The paracetamol preferably represents at least 2%, more preferably at least 5%, most preferably at least 8% or 10% or 20% or 25% or 28% or 30% or 35% or 40% or 50% or 60%, of the coformulation. The oligomeric or polymeric material is preferably hydrophobic; most preferably it is an ethyl cellulose. The amorphous phase

5   paracetamol is preferably stable, with respect to its crystalline form(s), for at least three months, preferably six months, more preferably nine or twelve or eighteen or twenty four or thirty six months, after its preparation, when stored at between 0 and 10°C. It is preferably also stable, for the same period, when stored at 25°C, more preferably also at 40°C.

10   Aspects of the invention can also provide methods for preparing the above described coformulations, using a SEDS™ process, as well as the use of a SEDS™ process to prepare the coformulations. In particular, the invention provides the use of a SEDS™ process to prepare a coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in

15   an amorphous as opposed to crystalline form, and in which the amorphous phase active substance is stable, with respect to its crystalline form(s), for at least three months after its preparation when stored at between 0 and 10°C. It also provides the use of a SEDS™ process to prepare a coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an

20   amorphous as opposed to crystalline form and in which the active substance represents at least 10% of the coformulation.

          Also provided is a pharmaceutical composition containing a coformulation according to the first, second or third aspect of the invention.

          The invention further provides a method for preparing a coformulation of an

25   active (preferably a pharmaceutically active) substance and a hydrophobic oligomeric or polymeric excipient, using a SEDS™ process, in which the active substance and the excipient are chosen so that the difference between their respective total specific solubility parameters, δ_s, is between -5 and +5, preferably between -2 and +2 and more preferably zero or close to zero. The excipient is preferably a cellulose or cellulose derivative such

30   as an ethyl cellulose. The invention provides the products of such a method, and the use of a SEDS™ process in it.

A further aspect of the invention provides a method for preparing a coformulation of an active (preferably pharmaceutically active) substance and an oligomeric or polymeric excipient, using an anti-solvent-induced particle formation process (preferably a SEDS™ process), wherein, under the operating conditions used,

5   the active substance is soluble in the chosen "anti-solvent" but the excipient is not. A preferred "anti-solvent" for this method is supercritical carbon dioxide. The active substance is preferably non-polar, as for instance the drug ketoprofen, and the excipient is preferably hydrophilic, for instance HPMC. Again the invention provides the products of such a method, and the use of a SEDS™ process in it.

10   A yet further aspect of the invention provides a method for preparing a coformulation of indomethacin and polyvinyl pyrrolidone, using an anti-solvent-induced particle formation process, preferably a SEDS™ process. The invention provides the products of such a method, and the use of a SEDS™ process in it.

In some cases, it appears that SEDS™ can yield active/excipient mixes of

15   sufficient intimacy that the initial "burst" of drug release, which tends to occur in the dissolution profiles of conventional systems, can be inhibited or even prevented. Certain coformulations according to the present invention can therefore be used as slow release drug formulations, providing a more uniform rate of drug release without the need for protective coatings or additional reagents. Examples include in particular coformulations

20   of water soluble active substances such as theophylline with relatively hydrophobic excipients such as ethyl cellulose.

This finding is particularly important since the coformulation of an active substance in its amorphous phase would normally be expected to *increase* its dissolution rate. Previous attempts to inhibit dissolution have instead typically involved placing

25   *physical* constraints on the active substance, such as by trapping its particles in a two-phase polymer matrix.

Thus, a further aspect of the invention provides a coformulation of an active (preferably a pharmaceutically active) substance and an oligomeric or polymeric excipient, comprising an intimate single-phase mixture of the active substance and the

30   excipient in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, from which the dissolution rate of the active substance in an aqueous medium is no higher for the first 30 minutes, preferably for the

first 60 or 90 or 120 minutes, than it is subsequently. Such a coformulation is again preferably prepared by a SEDS™ process.

Yet another aspect of the present invention provides a coformulation as defined above wherein the active substance is a COX-2 selective inhibitor. As used herein "COX-2 selective inhibitor" means an organic compound or pharmaceutically acceptable salt or solvate thereof which is capable of selectively inhibiting the COX-2 enzyme over the COX-1 enzyme.

The COX-2 selective inhibitor may be a diarylheterocycle. As used herein "diarylheterocycle" means an organic compound of the diarylheterocycle genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent atoms in a five or six-membered heterocycle or both of said phenyl rings directly attached to the same carbon atom of a C_{1-3} alkylidene linker, said C_{1-3} alkylidene linker further attached to one atom in said five or six-membered heterocycle.

The COX-2 selective inhibitor may be a diarylfuranone. As used herein "diarylfuranone" means an organic compound of the diarylfuranone genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent carbon atoms in a furanone moiety or both of said phenyl rings directly attached to the same carbon atom of a C_{1-3} alkylidene linker, said C_{1-3} alkylidene linker further attached to one carbon atom in said furanone moiety.

The COX-2 selective inhibitor may alternatively be a diarylpyrazole. As used herein "diarylpyrazole" means an organic compound of the diarylpyrazole genus (or a pharmaceutically acceptable salt or solvate thereof), comprising two substituted or unsubstituted phenyl rings each directly attached to adjacent atoms in a pyrazole moiety or both of said phenyl rings directly attached to the same carbon atom of a C_{1-3} alkylidene linker, said C_{1-3} alkylidene linker further attached to one atom in said pyrazole moiety.

The COX-2 selective inhibitor may alternatively be an arylpyridylpyridine. As used herein "arylpyridylpyridine" means an organic compound of the arylpyridylpyridine genus (or a pharmaceutically acceptable salt or solvate thereof), comprising one substituted or unsubstituted phenyl ring and one substituted or unsubstituted pyridyl moiety each directly attached to adjacent atoms in a pyridine ring or both said phenyl ring

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and pyridyl moiety directly attached to the same carbon atom of a C_{1-3} alkylidene linker, said C_{1-3} alkylidene linker further attached to one atom in said pyridine ring.

The COX-2 selective inhibitor is preferably selected from the group consisting of (Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one,

5   (Z)-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone and the compound of Formula (III):

(III)
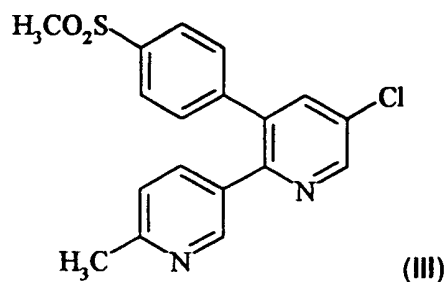
10

(Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one and (Z)-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene] dihydrofuran-2-one are COX-2 selective inhibitors useful for the treatment of acute and chronic pain.

15   *See* U.S. 5,807,873 and related applications incorporated by reference herein.

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is a COX-2 selective inhibitor approved for the treatment of osteoarthritis and rheumatoid arthritis and is marketed in the U.S. under the tradename CELEBREX® (celecoxib). *See, e.g.*, U.S. 5,466,823 and U.S. 5,563,165, incorporated by reference herein.

20   4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone is a COX-2 selective inhibitor approved for the treatment of osteoarthritis, treatment of primary dysmenorrhea and management of acute pain and is marketed in the U.S. under the tradename VIOXX® (rofecoxib). *See e.g.*, U.S. 5,474, 995, incorporated by reference herein.

The compound of Formula (II) is a COX-2 selective inhibitor being developed

25   for the treatment of acute and chronic pain. *See* WO 99/15503 and related applications incorporated by reference herein.

These and other COX-2 selective inhibitors falling within the biarylheterocycle genus or more particularly biarylfurananone and biarylpyrazole genera appear to have low aqueous solubility, suggesting suboptimal bioavailability. Their coformulation with oligomeric or polymeric excipients, in accordance with the present invention, can be

5   expected to enhance their bioavailability

The present invention will now be described, by way of example only, with reference to the following experiments and the accompanying figures, of which:

Figure 1 is a schematic illustration of apparatus usable to carry out methods, and obtain products, according to the invention;

10   Figures 2-5 are SEM (scanning electron microscope) photographs of some of the starting materials and products of Example I below;

Figures 6 to 8 show dissolution profiles for three of the systems investigated in Example I;

Figures 9 to 19 show plots of crystallinity against drug weight fraction for the

15   systems investigated in Example I;

Figures 20 to 24 are DSC (differential scanning calorimetry) traces for, respectively, crystalline indomethacin and a number of coformulations prepared in Example I, including after 24 months' storage;

Figures 25 and 26 are plots of $(\delta_s^d - \delta_s^p)$ against X (see Table 10 below) for some

20   of the systems investigated in Example I;

Figures 27 and 28 are SEM photographs of some of the products of Example II;

Figures 29 and 30 are plots of crystallinity against drug weight fraction for the products of Example II; and

25   Figure 31 is a plot of crystallinity against drug weight fraction for the products of Example III.

Examples

30

The following experiments demonstrate the use of a SEDS™ process to coformulate various drugs and polymers in accordance with the present invention. The

physicochemical characteristics of the products, in particular the degree (if any) of drug

crystallinity, the stability of the amorphous phase and the relative concentrations of the

drug and the polymer (ie, the drug "loading"), were tested and where possible

manipulated by altering the operating conditions and solvents present.

5   The drugs were chosen to cover a broad range of polarities, including the highly

apolar ketoprofen and, in ascending order of polarity, indomethacin, carbamazepine,

paracetamol, theophylline and ascorbic acid. These drugs were coformulated with both

hydrophobic (EC) and hydrophilic (HPMC) polymers.

           Ketoprofen was on the whole too soluble in supercritical carbon dioxide (the

10   chosen anti-solvent) to produce meaningful results, even under moderate processing

conditions. Surprisingly, however, it could be retained to a degree when coformulated

with HPMC.

           In an additional investigation, PVP was coformulated with the poorly water

soluble drug indomethacin.

15   Further experiments (Examples II and III) coformulated two cyclo-oxygenase-2

(COX-2) enzyme inhibitors with HPC and, in the case of Example II, a

polyoxypropylene-polyoxyethylene block co-polymer, Pluronic™ F87.

           In Example IV, the drug glibenclamide was coformulated with 75/25 DL-lactide-

co-caprolactone.

20

Experimental details

           The method used was essentially the SEDS™ process described in WO-

25   95/01221. It is envisaged that modifications of SEDS™, as described in that document,

WO-96/00610, WO-98/36825, WO-99/44733 and/or WO-99/59710, could be used to

similar effect.

           The apparatus is shown schematically in Figure 1, in which 1 is a particle

formation vessel; 2 is a device (eg, a filter) for retaining the particles formed; 3 is an oven

30   and 4 a back pressure regulator; and 5 is a nozzle for co-introducing, into the vessel 1, a

supercritical anti-solvent from source 6 and a target solution from source 7. The items

labelled 8 are pumps; 9 is a cooler, 10 a heat exchanger and 11 a pulse dampener. A

16

recycling system 12 allows solvent recovery at 13 (via needle valve 14), whilst returning carbon dioxide to the cooler 9 for re-use.

The nozzles employed at 5 were two-passage coaxial nozzles of the general form depicted in Figure 3 of WO-95/01221, typical dimensions being as described in that

5   document. Supercritical carbon dioxide was the chosen anti-solvent, introduced into a 50 ml particle formation vessel via the inner nozzle passage. The "target solution", ie, a solution of the drug or polymer, or more typically of both together, was introduced through the outer nozzle passage.

In situ mixing of separate drug and polymer solutions could have been achieved

10   using a nozzle having three or more coaxial passages, allowing the two solutions to meet at the nozzle outlet.

Selection of a suitable solvent depended on the properties of both drug and polymer, but particularly on the latter because of the potential difficulties of processing polymeric solutions and dispersions. Polymeric dispersions can exhibit very high

15   viscosities, even when dilute, whereas in "good" solvents the polymer matrix will relax and loosen, allowing both a greater degree of interaction and a lower viscosity, important respectively for the production of intimate drug/polymer mixtures and for the processing requirements of SEDS™ [8].

The analytical techniques employed in the experiments were as follows:

20

Scanning electron microscopy (SEM)

Particle size and morphology were investigated using an Hitachi™ S-520 scanning electron microscope (Hitachi, Japan). Aluminium stubs containing a small quantity of sample particulate were sputter-coated with a gold layer ~300Å thick and

25   viewed and photographed under varying magnifications.

Differential scanning calorimetry (DSC)

This technique was used to measure sample crystallinity, given that the lower the order of the crystal lattice the less energy required for melting the sample. DSC was used

30   to determine thermal profiles, to monitor the latent heat of fusion (ΔH_f), to identify any phase or polymorphic transitions and desolvation phenomena, and to determine melting points and glass transition temperatures.

17

A Perkin-Elmer™ DSC 7 (Perkin-Elmer Ltd, UK) was used. 1-5 mg samples were examined in pierced, crimped aluminium pans, under an atmosphere of nitrogen. The analytical temperature range depended on the drug investigated. Theophylline sublimed just above the melting point, causing difficulties in measuring endotherm peak

5   size. This problem was overcome by adopting a sealed pan method.

Relationships between product crystallinity and weight fraction of drug in the product were also investigated. Crystallinity was derived from the latent heat of fusion (ΔH_f), using the equation:

$$\% \text{ crystallinity} = \frac{\Delta H_f \text{ (coformulation)}}{\Delta H_f \text{ (100\% crystalline)}} \times \frac{100}{\text{Weight fraction of drug}}$$

10

X-ray diffraction (XRD)

This was also used to give a qualitative assessment of crystallinity. Samples

15   were analysed on a D5000 XRD (Siemens, Germany) between 5 and 30° 2θ.

UV spectrophotometry (Example I)

The weight fraction of drug in samples was measured with an Ultrospec™ 4000 spectrophotometer (Pharmacia Biotech, Cambridge, England), from reconstituted

20   solutions of the samples. The absorbance of the polymers was negligible at the wavelengths used.

Dissolution test (Example I)

Dissolution testing was carried out using a stirred vessel technique and UV

25   analysis. The apparatus consisted of a 1 litre round-bottomed vessel maintained at around 37°C in a water bath, stirred by paddle at 60 rpm. The medium was circulated using a peristaltic pump through a 10 mm flow cell. UV readings were taken every 30 seconds using an Ultrospec™ 4000 spectrophotometer (*supra*) and analysed for up to between 30 and 60 minutes.

Three systems were analysed: paracetamol/HPMC, theophylline/EC and

indomethacin/HPMC. The conditions for the individual systems were:-

Paracetamol/HPMC: 247 nm, 37±0.5°C, 500 ml distilled water.

Theophylline/EC: 273 nm, 37±1.0°C, 350 ml distilled water.

Indomethacin/HPMC: 235 nm, 37±0.5°C, 400 ml pH 7.00±0.02 0.05M

NaH_2PO_4 aqueous buffer.

A different medium was needed for the indomethacin system due to the drug's

poor water solubility. The chosen medium provided a compromise between observing

drug release within a practical time span and allowing sufficient discrimination to identify

true dispersions.

The release profile characteristics were compared with physical mixes to give an

indication of polymer/drug interaction and possible complex formation. The physical

mixes were prepared from pre-micronised drug ground (for 1 minute in a pestle and

mortar) together with the designated polymer. Samples were transferred to hard gelatine

capsules (size 4 clear/clear, weighted by 60:40 tin/lead wire coils) for analysis. The

capsules gave no significant absorbance in the analysis region.

Aerosizer-Aerodisperser™ particle size analyser (Example II)

Particle size analysis was carried out using a time-of-flight analyser (Aerosizer™

with Aerodisperser™, TSI Inc, USA). This instrument is capable of sizing dry powder

samples over the range 0.2-700 µm. The powder is dispersed in air and the air/particle

suspension is expanded through a nozzle into a partial vacuum. The air/particle stream

accelerates through a measuring region, where the particles pass through two consecutive

laser beams. Smaller particles experience a greater acceleration than larger ones and

hence move more rapidly between the two beams. From measurements of the time taken

to travel between the beams and the known density of the material, the Aerosizer™

software calculates the mean size distribution of particles present in the sample. The data

obtained complements SEM observations. No sample preparation is required.

HELOS Sympatec™ particle size analyser (Examples II and III)

This instrument uses laser diffraction to determine particle size distributions of

solid particulate materials. It is capable of measuring across the particle size range 0.1-

8750 µm. A dry powder sample is introduced, via a vibrating conveyor feeder, into a dry
dispersing unit. Here the powder and any agglomerates present are fully dispersed in air.
The dispersion of single particles is then propelled by compressed air and fed through the
measuring zone, where the particle stream interacts with a monochromatic high energy
5   beam from a He-Ne laser. The laser light is diffracted and detected by a multicomponent
photodetector. The intensity of the diffracted light is then converted into an electrical
signal, which is used to calculate the particle size distribution. Again, the data
complements SEM observations. No sample preparation is required.

10   **High performance liquid chromatography (HPLC) (Examples II and III)**

Compound (I) and (II) loadings were determined by HPLC using UV detection.
An isocratic method was followed, employing a single mobile phase (0.1% phosphoric
acid:acetonitrile (62:38 v/v), degassed for 20 minutes before use).

Quantification was by external standardisation. Two stock solutions of
15   Compound (I) with concentrations of 500 µgml^{-1} were prepared in the mobile phase.
Appropriate volumes were alternately taken and diluted with mobile phase to produce a
set of standard calibrants in the nominal range 2 to 10 µgml^{-1}. Aliquots of prepared
sample solutions, diluted if necessary, were then submitted to HPLC analysis,
interspersed with the calibrant solutions. Using the following nominal conditions a
20   chromatogram was generated.

Pump:	Capable of delivering 1.1 mlmin^{-1}
Sample size:	20 µl (ATI Unicam™ autosampler)
Column:	150 x 4.6 mm, ZORBAX™, RX-C8, 5 µm
Column temperature:	30°C
Flow rate:	1.1 mlmin^{-1}
Detector/wavelength:	Jasco™ UV-975 / 220 nm
Peak response:	Area
Cycle time:	Typically 17 minutes

All peak area measurements and calculations were performed using Borwin™ chromatography software Version 1.22.01.

5   Example I

The materials used in this series of experiments were as follows; their polarities and solubility parameters are listed in Table 1 below.

Material	Supplier	Grade
L-ascorbic acid	Sigma Chemical Co, St Louis, Missouri, USA	General laboratory reagent
Carbamazepine	Sigma	Ditto
Indomethacin	Sigma	Ditto
Ketoprofen	Sigma	Ditto
Paracetamol	Sigma	99.0%+
Theophylline	Sigma	Anhyd. 99%+
EC	Colorcon, Dartford, England	7 cps
HPMC	Shinetsu Chemical Company, Tokyo, Japan	3 cps (603)
PVP	Sigma	Av. mol. wt. 10,000
Dichloromethane	BDH (Merck), Poole, England	AnalaR 99.5%+
Chloroform	BDH	AnalaR 99.0-99.4%
Ethanol	BDH	AnalaR 99.7-100%
Ethanol	Rathburn Chemicals Ltd, Walkerburn, Peebleshire, Scotland	HPLC
Methanol	BDH	AnalaR 99.8%+
Sodium dihydrogen orthophosphate	Sigma	99.0%+

(De-ionised water was obtained from a Jencons Waterstill™ 4000X.)

10

Material	Chemical structure
L-ascorbic acid	

21

$$\text{CH}_2\text{OH}$$
$$\text{HC—OH}$$
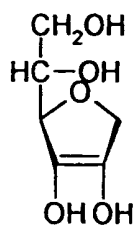
Carbamazepine
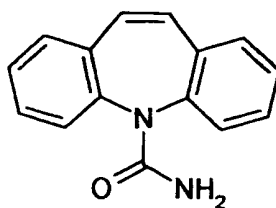
5

Indomethacin
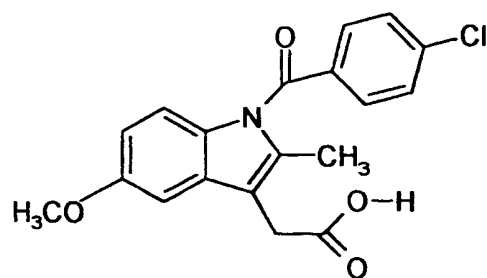
10　　Ketoprofen
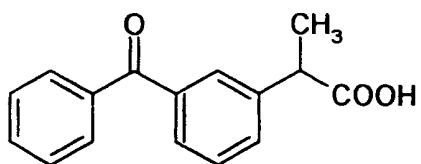
Paracetamol

(US acetaminophen)
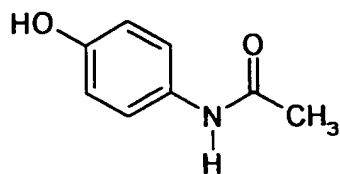
$$HO\text{—}\bigodot\text{—}N(H)\text{—}C(=O)\text{—}CH_3$$

Theophylline

$$H_3C\text{—}N\text{—}\cdots\text{—}O$$

5   Ethyl cellulose (EC)

$$\left[\text{—}O\text{—}\underset{OC_2H_5}{\overset{CH_2OC_2H_5}{\bigodot}}\text{—}\right]_n$$

Hydroxypropyl methyl

Cellulose (HPMC)

$$\left[\text{—}O\text{—}\underset{OR}{\overset{CH_2OR}{\bigodot}}\text{—}O\text{—}\underset{CH_2OR}{\overset{OR}{\bigodot}}\text{—}\right]_n$$

R is H, CH$_3$ or [CH$_3$CH(OH)CH$_2$]
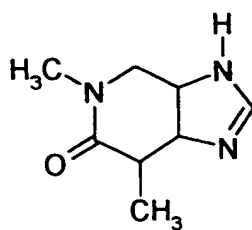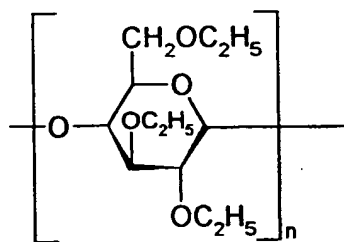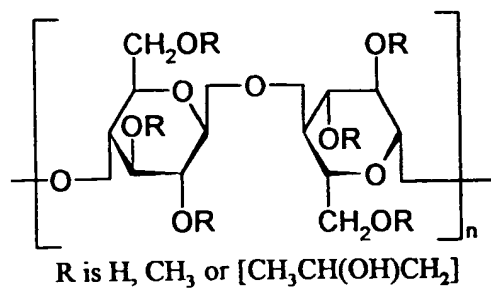
10

Polyvinyl

Pyrrolidone (PVP)
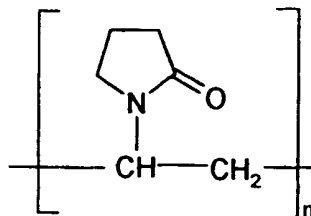
Table 1   **Polarity and solubility parameters of drugs and polymers studied***

Material	Polarity	δ_d (MPa$^{\frac{1}{2}}$)	δ_p (MPa$^{\frac{1}{2}}$)	δ_h (MPa$^{\frac{1}{2}}$)	δ_s^+ (MPa$^{\frac{1}{2}}$)	δ_t (MPa$^{\frac{1}{2}}$)
Ethyl cellulose	0.34	16.7	2.9	11.7	12.4	20.6
Hydroxypropyl methyl cellulose	0.69	13.7	6.5	14.9	16.3	21.3
Ascorbic acid	0.71	21.0	14.0	30.0	33.1	39.2
Carbamazepine	0.23	22.0	7.6	9.6	12.2	25.2
Paracetamol	0.40	21.1	8.5	15.0	17.2	27.3
Indomethacin	0.19	21.9	5.6	9.1	10.7	24.4
Theophylline	0.53	17.4	13.1	12.8	18.3	25.2

5

*Values obtained from published literature

$^+\delta_s = (\delta_p^2 + \delta_h^2)^{\frac{1}{2}}$

10   In Table 1, δ_d, δ_p and δ_h are the partial solubility parameters representing dispersive, polar and hydrogen bonding effects respectively; δ_t is the total solubility parameter, where $\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2$ [9]; δ_s is the total specific (ie, polar and hydrogen bonding) solubility parameter.

     The principal operating conditions (temperature, pressure, fluid flow rates and nozzle orifice diameter) were manipulated and optimised for each drug/polymer system.

15   Different drug:polymer concentration ratios were also tested.

It was found that temperatures in the range 34-50°C and pressures between 80 and 100 bar were preferable for processing these polymers. Anti-solvent:target solution flow rate ratios (into the particle formation vessel) were between 66:1 and 200:1, ie, an anti-solvent flow rate of 20 ml/min was used with target solution flow rates of between

5   0.1 and 0.3 ml/min.

Nozzle outlet internal diameters were between 100 and 500 μm, 100 μm being preferred over those greater than 200 μm.

A 1:1 mixture of ethanol and dichloromethane (or 1:1 ethanol/chloroform in the case of PVP) was used as the drug/polymer solvent. This yielded dispersions of suitably low viscosity, enabling processing without significant nozzle blockage. Similarly, ethanol

10   was found to produce low viscosity dispersions for the EC systems. A polymer concentration of 0.5% w/v provided a balance between the ability to pump the solution at a moderate back pressure and an acceptably high material throughput.

To facilitate processing, the polymers used were selected from the lower

15   molecular weight fractions - 3 cps HPMC, 7 cps EC and PVP of average molecular weight 10,000.

Results & discussion

The results of the various experimental runs (in particular yield, morphology and

20   drug loading) are summarised in Tables 2 (ascorbic acid), 3 (carbamazepine), 4 & 5 (indomethacin), 6 & 7 (ketoprofen), 8 (paracetamol) and 9 (theophylline), appended. The tables also indicate the operating conditions (temperature and pressure within the particle formation vessel, fluid flow rates, target solution concentration and nozzle tip (outlet) diameter) for each run.

25   The products were in the form of finely dispersed particulates; all were non-cohesive, easy-flowing powders with good handling properties. Their morphology was assessed using SEM, which revealed the non-crystalline products typically as fine, agglomerated, roughly spherical particles of the order of 0.05-1 μm diameter. The homogeneity in the appearance of the particles suggested they comprised molecular-level

30   dispersions. Above the amorphous limits detected, mixtures of such web structures with additional, larger drug crystals were observed in many cases.

Figures 2 to 5 are SEM photographs of some of the starting materials and products of the experiments. Specifically, Figure 2 shows the indomethacin raw material (at 2000x magnification); Figure 3 shows the amorphous indomethacin/HPMC product of experimental run RASE 21 (2000x magnification); Figure 4 shows the paracetamol raw material (200x magnification) and Figure 5 shows the amorphous paracetamol/HPMC product of experimental run RASF 34 (1000x magnification).

Dissolution tests

Figures 6 to 8 show dissolution profiles for three of the systems investigated, namely paracetamol:HPMC (Figure 6), theophylline:EC (Figure 7) and indomethacin:HPMC (Figure 8). The labelling corresponds to that used in Tables 2-9 for the various experimental runs; X (%) is the maximum concentration of the amorphous phase of the drug prior to the detection of crystallinity. In all three systems, there were significant differences in drug release rates between the SEDS™-coformulated products and purely physical mixes of the relevant drug and polymer, suggesting that the products of the present invention had been formed as intimate molecular level dispersions of a drug in a polymer matrix. For instance, the release of theophylline was significantly inhibited by coformulating it with EC according to the invention, that of paracetamol was also slightly inhibited by coformulation with HPMC, whilst the dissolution rate of indomethacin was increased on coformulation with HPMC (including one sample above the amorphous detected limit).

Degree of crystallinity

Plots of drug crystallinity (determined by DSC) against drug weight fraction are shown in Figures 9 to 19. The systems illustrated are ascorbic acid/EC, ascorbic acid/HPMC, carbamazepine/EC, carbamazepine/HPMC, indomethacin/EC, indomethacin/HPMC, indomethacin/PVP, paracetamol/EC, paracetamol/HPMC, theophylline/EC and theophylline/HPMC respectively.

Although it depended very much on the drug and polymer involved, in general the proportion of amorphous to crystalline drug present in the SEDS™ products was found to be higher than that achieved using conventional processing techniques such as evaporation and coprecipitation from solvent systems [1]. For instance, maximum

26

amorphous phase concentrations for indomethacin were 25±5% with EC, 35±5% with HPMC and 60±5% with PVP. Up to 10-15% amorphous ascorbic acid was achieved in coformulation with EC, and up to 35-40% with HPMC (Figures 9 and 10). (Note that drug concentration *ranges* are quoted at the limit of the amorphous/crystalline state boundary, due to the limitations of the method of quantifying crystallinity by DSC and the limited number of data points around the phase change concentration.)

These results are of particular significance for poorly water soluble pharmaceuticals, for which the amorphous form is generally preferred because of its superior dissolution rate.

Physical and chemical stability

The medium to long term storage stability of several of the Example I products was investigated. In all cases the physical properties of the samples were unchanged even after up to 24 months' storage; the samples remained free flowing and easy to handle.

Chemical stability (in terms of amorphous phase contents) was assessed using DSC. Looking firstly at the indomethacin/PVP system, the drug in its crystalline form exhibits a peak in DSC profiles at 150-165°C, when analysed at a scanning rate of 20°C/min. This peak shifts to lower temperature in coformulated indomethacin/PVP systems. Figures 20 and 21 show DSC profiles for, respectively, the crystalline raw material and the indomethacin/PVP system prepared in experimental run RASE 64. The peak at 139°C in Figure 20 indicates the presence of crystalline indomethacin in the sample (which contained 78% w/w indomethacin, with 30% crystallinity).

The indomethacin/PVP samples prepared in experimental runs RASE 70, RASE 69, RASE 62, RASE 66 and RASE 63 (containing 16, 20, 48, 51 and 62% indomethacin respectively), were assessed initially and after both 12 and 24 months' storage in a desiccator at between 2 and 8°C. The DSC results indicated no crystallinity in any of the samples even after 24 months. An example DSC profile for the RASE 63 sample at 24 months is shown in Figure 22; the absence of the 139°C peak indicates an absence of crystalline indomethacin.

Three theophylline/EC systems were also tested, after storage at ambient temperature and without desiccation. The DSC profiles obtained after 24 months for the products of runs RASH 6, LSDA 52 and RASH 14 (containing 9, 17 and 27%

theophylline respectively, in each case 100% amorphous) again lacked definite peaks, indicating no detectable drug crystallinity. An example DSC profile, for the RASH 14 sample, is shown in Figure 23.

In a similar experiment, the stabilities of four of the paracetamol/HPMC

5   products were tested over a 24 month storage period. The storage conditions were as for the theophylline/EC systems. The 24 month DSC profiles for the products of experimental runs RASF 31, RASF 27, RASF 97 and RASF 40 (containing 19, 20, 21 and 29% paracetamol respectively, in each case 100% amorphous) indicated an absence of crystallinity. Figure 24 is an example DSC profile, for the RASF 40 sample.

10   Thus, coformulations according to the invention, made by a SEDS™ process, appear to possess excellent long term storage stability, with respect both to their physical properties and to re-crystallisation of the active substance.

With regard to the above stability data, it is of note that many of the systems tested were close to the point of inflexion on the graphs of crystallinity versus drug

15   loading. In other words, they were systems containing the maximum possible drug loading before the onset of crystallinity. Other products of the invention, containing lower drug loadings, would if anything be more stable under the same storage conditions.

Solubility effects

20   A relationship was observed, in the systems containing the hydrophobic polymer ethyl cellulose, between the amorphous phase drug concentration and the total specific solubility parameters δ_s ($\delta_s = (\delta_p^2 + \delta_h^2)^{1/2}$ - see Table 1) of the reagents. Insofar as could be inferred from the systems studied, the trend was towards the maximum concentration of amorphous phase (and thus also the maximum drug:polymer interaction) being achieved

25   when the δ_s of the drug and the polymer were equivalent or substantially so.

It appears that drug/polymer dispersion, and intermolecular/interpolymeric chain mixing and interaction, can be maximised by choosing the reagents so that ($\delta_s^d - \delta_s^p$) is zero or close to zero (where δ_s^d and δ_s^p represent the total specific (ie, polar and hydrogen bonding) solubility parameters for the drug and polymer respectively). These systems

30   would be expected to contain the maximum amount of amorphous phase drug, lower amorphous phase levels occurring as ($\delta_s^d - \delta_s^p$) attained either a positive or a negative value.

28

Table 10 lists calculated values of $(\delta_s^d - \delta_s^p)$ for the systems studied, together with values of X% (mid-point and range).

Table 10

Drug/Polymer	$(\delta_s^d - \delta_s^p)$	X(%) Midpoint	Range
Ascorbic acid/EC	20.7	12.5	10-15
Ascorbic acid/HPMC	16.8	37.5	35-40
Carbamazepine/EC	-0.2	25.0	20-30
Carbamazepine/HPMC	-4.1	32.5	25-40
Paracetamol/EC	4.8	6.0	1-12
Paracetamol/HPMC	0.9	30.0	25-35
Indomethacin/EC	-1.7	23.0	18-28
Indomethacin/HPMC	-5.6	40.0	35-45
Theophylline/EC	5.9	25.0	20-30
Theophylline/HPMC	2.0	12.5	5-20

The Table 10 data are plotted in Figures 25 and 26. The maximum amorphous phase contents found for drug/EC systems, with the exception of paracetamol/EC, seem to be in accord with the hypothesis (Figure 25), showing a maximum of approximately 27% amorphous content at $\delta_s^d - \delta_s^p = 0$. In contrast, for the drug/HPMC system (Figure 26), a minimum is observed at the zero point, with the paracetamol/polymer system again deviating from the trend.

The systems containing paracetamol deviate from the trends exhibited by the other drugs. Polar systems have a greater tendency to exhibit irregular solution behaviour. Furthermore, if a molecule contains at least two active groups with differing hydrogen bonding abilities, this can lead to anomalous solubility behaviour. Commonly referred to as the "chameleonic effect", this is a combined effect of the solubility parameter and solute-solvent and solvent-solvent hydrogen bonding. Paracetamol is known to form

irregular solutions in polar solvents [10-12] and contains the functional groups -OH and -
NH-, which leads to varying behaviour dependent on the solvent environment.

It is of note that attempts to form amorphous paracetamol using conventional
particle formation techniques have proved unsuccessful, this being attributed to the high

5   crystallinity and crystal energy of the drug. However, using SEDS™ to coformulate
paracetamol with for instance HPMC, a particulate product containing between 25 and
35% of the amorphous drug can be prepared.

10   Example II

This series of experiments demonstrates the coformulation, using SEDS™, of a
cyclo-oxygenase-2 (COX-2) inhibitor of the formula (I):
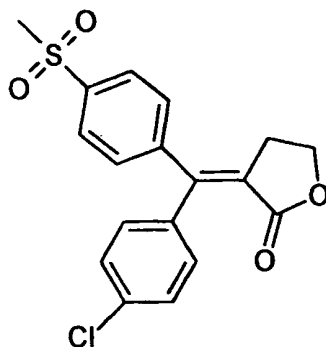
((Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulfonyl)methylene]-dihydrofuran-2-one) with:

15

(a) hydroxypropyl cellulose (HPC):

Structural Formula:
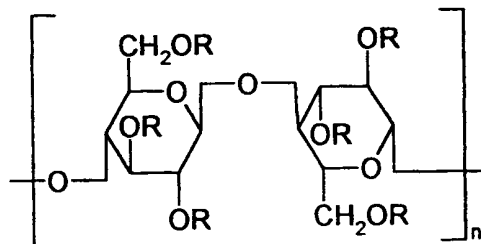
Where R is H or [-CH$_2$-CH(CH$_3$)-]$_m$H

30

and:

(b) "Poloxamer 237" (P-237), also known as Pluronic™ F87, which is a polyoxypropylene-polyoxyethylene block copolymer of the chemical formula

5    $HO(C_2H_4O)_{64}(C_3H_6O)_{37}(C_2H_4O)_{64}H$.

The reagents used in the experiments were analytical or HPLC grade.

For (a), the solvent used was a mixture of DCM and ethanol (1:1), which could dissolve both the drug and the polymer together. The (HPC + drug) concentration was varied between 0.5 and 4.5% w/v and the DCM:ethanol ratio was altered where

10   appropriate to increase solution saturation. The ethanol helped to lower the viscosity of the HPCdispersion.

The operating conditions for (a) were 90 bar and between 50 and 70°C. Higher temperatures facilitated solvent extraction. CO_2 flows of up to 20 ml/min were used, with target solution flows of as low as 0.1 ml/min. The conditions for each experimental

15   run are summarised in Tables 11 and 12, appended.

For (b), the operating temperature was 35°C (due to the relatively low melting point of the polymer) and the pressure was varied between 75 and 100 bar. DCM was used as a solvent for both Compound (I) and the polymer together, with solution concentrations between 1 and 3% w/v. The CO_2 anti-solvent flowed at 18 ml/min and

20   the target solution at between 0.1 and 0.2 ml/min. Table 13 (appended) summarises the operating conditions for each run.

In both sets of experiments, nozzle outlet diameters of 100, 200, 400 and 750 μm were employed, and either a 50 ml or in some cases a 500 ml particle formation vessel.

Results & discussion – Compound (I) and HPC

25   The results are given in Tables 11 and 12, appended. The best yields and particle sizes were obtained in run 14, using 85% w/w of Compound (I) – this gave a 95% yield of free flowing rounded/plate-like particles with an average diameter of 3.8 μm (Figure 27, SEM taken at 4000x magnification). At 30% w/w HPC (run 17), a 96% yield was obtained but the particles were more flake-like and agglomerated, their average size being

30   13.1 μm. HPC concentrations of 50 and 80% w/w gave large (20.7 μm) coral-like

31

agglomerates (runs 21 (Figure 28, SEM taken at 2000x magnification) and 22). In all

runs the recovery of Compound (I) was greater than 90%.

Generally, nozzle blockages were reduced at lower concentrations (eg, about 80%

w/w or lower) of Compound (I). For some runs, a 50 ml vessel soon clogged with

5   precipitated solids; a 500 ml vessel was substituted to eradicate this problem.

Particle agglomeration (and hence large particle sizes) could generally be reduced

by decreasing the process throughput, for instance by reducing the concentration and/or

flow rate of the drug/polymer solution (whilst still maintaining a near saturated solution).

Results & discussion – Compound (I) and P-237

10   The results are given in Table 13, appended. The smallest particles of pure

Compound (I) were produced in run 38, using a 2% w/v target solution with a flow rate

of 0.15 ml/min. These conditions were used to produce coformulations for dissolution

testing, as well as a control batch of pure Compound (I).

The recovery of Compound (I) in all samples was 100%.

15

Degree of crystallinity

Products were subjected to DSC analysis to determine the degree of crystallinity

in the Compound (I) present. The results, as a function of drug concentration, are shown

in Tables 14 and 15 below, for the HPC and P-237 systems respectively, and are

20   illustrated graphically in Figures 29 and 30 respectively.

Table 14 -

Crystallinity levels in HPC systems

Concentration of Compound (I) (% w/w) (by HPLC)	ΔH_f coformulation J/g	% Crystallinity
Unprocessed Compound (I)	96.1	100
100	94.2	98.1
100	94.0	97.8
100	94.2	98.0

88	78.0	92.2
86.7	75.1	90.2
79	73.9	97.3
78.6	77.7	102.9
64.5	54.9	88.6
50	26.9	56.1
43.6	31.7	75.7
26.7	5.1	20.0
20	0	0

Table 15 -

Crystallinity levels in P-237 systems

Concentration of Compound (I) (% w/w) (by HPLC)	ΔH_f coformulation J/g	% Crystallinity
Unprocessed Compound (I)	96.0	100
100	93.6	97.4
86.2	64.9	78.4
85	66.4	81.4
71.3	48.1	70.3
70.7	46.6	68.7
53.7	20.8	40.3
20	0	0.0

The results for both systems indicate that crystallinity is significantly reduced as polymer content increases. The reduction is nearly linear for the P-237 system, but for HPC a polymer content of at least 20% w/w is needed before crystallinity levels start to decrease. For both systems, a 100% amorphous product was achieved at drug loadings of 20% w/w or less.

33

Physical and chemical stability

A representative sample containing 20% w/w Compound (I) and 80% w/w P-237, produced using a SEDS™ process as described above, was stored for 13 months in a screw-top glass jar, under ambient conditions (10-27°C) and in the dark. At the end of this storage period the sample was found to have retained its initial physical properties, ie, it was still a free-flowing, easily handled powder containing discrete particles. It had also retained its 100% amorphous nature (assessed using DSC).

Example III

This series of experiments demonstrates the coformulation, using SEDS™, of a COX-2 inhibitor of the formula (II):

(II)
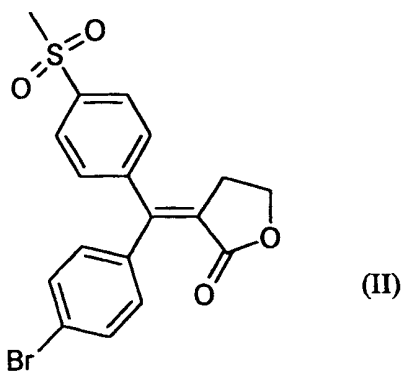
((Z)-3-[1-(4-bromophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one) with HPC.

Apparatus similar to that used in Examples I and II, but scaled up 10 fold, was used to carry out SEDS™ particle formation. Both Compound (II) and HPC (as used in Example II) were dissolved in acetone, at an optimum concentration of 2.0% w/v. The preferred operating temperature was 60°C and the pressure 120 bar. The optimum target solution flow rate was 1.0 ml/min, that for the supercritical carbon dioxide anti-solvent 200 ml/min. Products containing 10%, 20%, 30%, 50% and 70% w/w Compound (II)

were prepared using these conditions, the exact conditions for each run being summarised in appended Table 16.

For some runs, as indicated in the table, a lower molecular weight (80,000) grade of HPC was used.

Experiments were also carried out using DCM:ethanol (35:65 v/v) as the solvent, a solution concentration of 1.0% v/v, an operating temperature and pressure of 50°C and 90 bar respectively, a target solution flow rate of 1.0 ml/min and a supercritical carbon dioxide flow rate of 200 ml/min. The operating conditions for each run are summarised in Table 17, appended; a product containing 90% w/w Compound (II) was successfully prepared.

Results & discussion

The results are given in the appended Tables 16 and 17. Sample crystallinity was assessed in each case by DSC; the results are shown in Table 18 below and represented graphically in Figure 31 (plot of crystallinity against drug loading).

Table 18

Compound (II) Conc. (% w/w)	Latent heat of fusion Coformulation (J/g)	% Crystallinity	Run N°
Starting material	74.84	100	N/A
25	5.6	29.6	17
25	6.2	33.3	17
30	10	44.4	18
90	64.7	96.1	19
50	31.6	84.5	20
70	48.9	93.3	23
85	58.6	92.2	9
90	63.3	94	24
10	0	0	25
15	0	0	10
20	0	0	13

Thus, the products containing 20% w/w Compound (II) or less (run numbers 10, 13 and 25) had 0% crystallinity. After storage for approximately three months in screw top glass bottles, at ambient temperature (10-27°C) and in the dark, these samples were found to have retained their 100% amorphous nature. They were also still free-flowing,

5   easily handled powders, as initially.

Example IV

This series of experiments demonstrates the coformulation, using SEDS™, of

10   glibenclamide (1-{4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulphonyl}-3-cyclohexylurea, an anti-diabetic drug) and 75/25 DL-lactide-co-caprolactone (Birmingham Polymers, England).

Supercritical nitrogen was used as the anti-solvent, since supercritical carbon dioxide would plasticise the amorphous polymer excipient. The glibenclamide was

15   dissolved in methylene chloride. The anti-solvent flow rates were between 15 and 25 litres min⁻¹, those for the drug solution between 0.05 and 0.1 ml min⁻¹. A 500 ml particle formation vessel was used, at an operating temperature of between 35 and 60°C and a pressure of 100 bar.

20   *Results & discussion*

Coformulations having drug:polymer ratios of between 1:1 and 9:1 were successfully produced under the above conditions. XRD analysis confirmed that although the glibenclamide raw material was crystalline, all of the SEDS™ products contained 100% amorphous phase drug.

25   For all of the coformulations, residual solvent levels (measured using headspace gas chromatography (Varian™)) were below 300 ppm, surprisingly low in view of the poor mass transfer properties of supercritical nitrogen relative to supercritical carbon dioxide.

30

Appendix

There now follow Tables 2-9 (Example I), 11-13 (Example II) and 16 and 17 (Example III), referred to above.

5

Ascorbic Acid Result Table 2

Experiment	Drug Conc (%w/v)	Polymer	Polymer Conc (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle np diameter (μm)	Yield (%)	Comments	Morphology by SEM	DSC Peaks (ΔH - J/g)	% Drug in Product by UV (Wt.%)
RASF79	0.2	EC 10cps	0.50	Ethanol	0.3	20	34	120	100	58	Fine particulate	ND	23.0	50.1
RASF80	0.5	EC 10cps	0.50	Ethanol	0.3	20	34	80	100	50	Fine particulate, large nozzle blocks	ND	108.4	50
RASF81	0.5	EC 10cps	0.20	Ethanol	0.3	20	34	80	100	ND	CO2 pump problem, fine particulate	ND	176.5	75
RASF82	0.4	EC 10cps	0.30	Ethanol	0.3	20	34	80	100	63	Fine particulate	ND	123.7	57.1
RASF83	0.0	EC 10cps	0.60	Ethanol	0.3	20	34	80	100	73	Fine particulate	ND	2	5
RASF96 (SW)	0.1	EC 7cps	0.50	Methanol	0.2	20	34	80	100	62	Fine white particulate	ND	3.72	3.2
RASF97 (SW)	0.1	EC 7cps	0.50	Methanol	0.2	20	34	80	100	40	Fine white particulate	ND	29.24	17.2
RASF98 (SW)	0.2	EC 7cps	0.50	Methanol	0.2	20	34	80	100	29	Fine white particulate	ND	51.29	21.1
RASF99 (SW)	0.2	EC 7cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	100	40	Fine white particulate	ND	64	39.3
LSDA18R	0.2	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.3	20	34	80	100	61	Fine white powder	Aggregates	None	24
LSDA19	0.5	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.3	20	34	80	100	71	Fine white powder	Aggregates	96	48
LSDA20	1.0	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.3	20	34	80	100	81	Fine white powder	Aggregates	123	69
LSDA21	1.5	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.3	20	34	80	100	41	Fine off-white powder	Aggregates (0.5 - 0.5μm)	182	74
LSDA31	4.5	EC 10cps	0.50	Ethanol	0.3	20	34	80	100	58	Fine off-white powder	ND	226	86
LSDA32	4.5	EC 10cps	0.50	Ethanol	0.3	20	34	80	300	98	Fine off-white powder	ND	221	91
LSDA33	4.5	EC 10cps	0.50	Ethanol	1.3	20	34	80	500	64	Fine off-white powder	ND	222	91
LSDA34	2.0	EC 10cps	0.50	Ethanol	0.3	20	34	80	100	63	Fine off-white powder	ND	222	73
LSDA49	0.1	EC 10cps	0.50	Ethanol	0.3	20	34	80	100	47	Fine white powder	ND	24	18
LSDA50	0.1	EC 10cps	0.50	Ethanol	0.3	20	34	80	100	66	Fine white powder	ND	None	5

NA - Not applicable,   ND - Not determined

All experiments used a two component nozzle

Carbamazepine Results Table 3

Experiment	Drug Conc (%w/v)	Polymer	Polymer Conc. (%w/v)	Solvent	Solution Flow Rate (ml/min)	Pressure (bar)	CO2 flow (ml/min)	Temp °C	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm by SEM)	Morphology (by SEM)	DSC Peaks (ΔH J/g)	% Drug in Product by UV (Wt.%)
LSDA6	2.0	N/A	0	Ethanol	0.2	80	20	50	100	61	Fine white powder	ND	Acicular with some agglomerates	101	NA
LSDA7	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	100	38	Fine white powder	ND	Acicular with some agglomerates	19	41
LSDA8	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	58	Fine white powder	ND	Acicular	47	59
LSDA9	0.25	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	48	Fine white powder	ND	Acicular with some agglomerates	22	42
LSDA10	1.0	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	85	Fine white powder	ND	Acicular	79	64
LSDA11	0.167	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	45	Fine white powder	0.5 x 0.5	Aggregates with some acicular	None	25
LSDA12	1.5	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	95	Fine white powder	ND	Acicular	87	87
LSDA13	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	89	Fine white powder	ND	Acicular	26	43
LSDA14	0.25	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	80	Fine white powder	ND	Acicular	18	29
LSDA15	1.0	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	94	Fine white powder	ND	Acicular	53	60
LSDA16	0.167	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	70	Fine white powder	ND	Acicular with some agglomerates	None	24
LSDA17	1.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	89	Fine white powder	ND	Acicular with some agglomerates	58	69
LSDA38	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	85	Fine white powder	ND	ND	None	24
LSDA40	1.167	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	94	Fine white powder	ND	ND	68	70
LSDA42	0.215	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	500	49	Fine white powder	ND	ND	13	30
LSDA54	0.215	HPMC	0.5	Ethanol / DCM (1:1)	0.2	80	20	50	200	82	Fine white powder	ND	ND	None	28

A two-component nozzle was used in all experiments

NA - Not applicable,   ND - Not determined

Indomethacin Result Table 4

Experiment	Drug Solvent	Drug Conc (%w/v)	Polymer	Polymer Conc (%w/v)	Polymer Solvent	Solution Flow Rate (ml/min)	CO2 Flow Rate (ml/min)	Temp (°C)	Pressure (bar)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH-J/g)	% Drug in Product by UV (Wt%)
RASE2	Ethanol	2	NA	0	NA	0.2	15	50	100	100	91	Mass of fine strands	10×1	fibres	ND	NA
RASE3	Acetone	2	NA	0	NA	0.2	15	50	100	100	73	Mass of fine particulate	15×2	Acicular	ND	NA
RASE18	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	39	Fine off-white particulate	<0.1×0.1	Aggregates	None	15
RASE19	Ethanol/DCM(1:1)	0.25	HPMC (3cps)	0.75	Ethanol/DCM(1:1)	0.2	20	37	80	500	77	Fine off-white particulate	<0.1×0.1	Aggregates	None	13
RASE20	Ethanol/DCM(1:1)	0.25	HPMC (3cps)	0.75	Ethanol/DCM(1:1)	0.2	20	50	100	500	15	Fine off-white particulate	0.1×0.1	Aggregates	None	9
RASE21	Ethanol/DCM(1:1)	0.25	HPMC (3cps)	0.75	Ethanol/DCM(1:1)	0.2	20	50	80	500	62	Pale yellow fine particulate	1×1	Amorphous	None	27
RASE26	Ethanol/DCM(1:1)	0.25	HPMC (3cps)	0.75	Ethanol/DCM(1:1)	0.2	20	50	80	500	63	Pale yellow fine particulate	0.5×0.5	Aggregates	None	17
RASE27	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	50	80	500	64	Fine off-white particulate	0.5×10 & 1×1	Acicular & amorphous	0.7	55
RASE30	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	50	80	500	39	Very fine white particulate with yellow cob	Wide variations	Aggregates, acicular & fibres	43.0	63
RASE31	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	11	Fine off-white particulate	0.1×0.1 & 100×0.1	Acicular & fibres	0.1	22
RASE32	Ethanol/DCM(1:1)	0.75	HPMC (3cps)	0.25	Ethanol/DCM(1:1)	0.2	20	37	80	500	73	Fine white particulate with crystals	50×10, 50×1, 50×0.2	Tubular, acicular & fibres	<20 (135°C), 13.1 (160°C)	89
RASE33	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.1	20	37	80	500	64	Fine off-white particulate	Wide variations	Tubular, acicular, aggregates & fibres	0.1	38
RASE34	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.1	20	37	80	500	23	Fine off-white particulate	0.5×0.5	Amorphous	None	13
RASE35	Ethanol/DCM(1:1)	0.5	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	72	Fine off-white particulate	0.1×0.1	Amorphous	None	5
RASE36	Ethanol/DCM(1:1)	0.167	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.1	20	37	80	500	73	Fine off-white particulate	0.1×0.1	Amorphous aggregates	None	10
RASE37	Ethanol/DCM(1:1)	0.167	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	12	Fine off-white particulate	0.2×0.2	Amorphous aggregates	None	14
RASE38	Ethanol/DCM(1:1)	0.33	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.1	20	37	80	200	41	Fine off-white particulate	0.2×0.2	Amorphous aggregates	None	13
RASE39	Ethanol/DCM(1:1)	0.75	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	200	61	Fine off-white particulate	Wide variations	Aggregates, acicular & fibres	12.2	51
RASE40	Ethanol/DCM(1:1)	0.75	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	64	Fine off-white particulate	0.5×0.1 & 30×0.1	Amorphous & fibres	39.1	67
RASE41	Ethanol/DCM(1:1)	0.75	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	40	Fine off-white particulate	0.1×0.1	Amorphous aggregates	None	11
RASE42	Ethanol/DCM(1:1)	0.33	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.1	20	37	80	500	39	Fine off-white particulate	0.05×0.05	Amorphous aggregates	None	17
RASE43	Ethanol/DCM(1:1)	0.33	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	50	500	73	Pale yellow fine particulate	0.5×0.5, 5×0.5 & 3.5×0.5	Aggregates, acicular & fibres	19.6	42
RASE44	Ethanol/DCM(1:1)	0.33	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	50	80	500	74	Pale yellow fine particulate	15×10, 0.5×0.5, 20×0.5, 10×0.2	Amorphous(? open), acicular & fibres	20.7	51
RASE45	Ethanol/DCM(1:1)	0.41	HPMC (3cps)	0.5	Ethanol/DCM(1:1)	0.2	20	37	80	500	51	Fine off-white particulate	<0.1×0.1	Amorphous aggregates	None	12

NA - Not applicable. ND - Not determined

A two-component nozzle was used in all experiments

40

Indomethacin Result Table 5

Experiment	Drug Solvent	Drug Conc. (%w/v)	Polymer	Polymer Conc. (%w/v)	Polymer Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle up diameter (µm)	Yield (%)	Product Description	Size (µm by SEM)	Morphology (by SEM)	DSC Peaks (ΔH-J/g)	% Drug in Product by UV (W/W%)
RASE38	Ethanol	0.5	EC (7cps)	0.5	Ethanol	0.1	20	37	80	100	12	Fine yellow particulate	100 x150	Amorphous pitted chunks	None	34
RASE39	Ethanol	0.5	EC (7cps)	0.5	Ethanol	0.05	20	37	80	100	19	Fine yellow particulate	100 x150	Amorphous pitted chunks	None	46
RASE40	Ethanol	0.25	EC (7cps)	0.25	Ethanol	0.1	20	37	80	100	19	Fine yellow particulate	100 X 50	Amorphous pitted chunks	None	41
RASE42	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol / Chloroform	0.2	20	37	80	100	23	Fine yellow particulate with yellow flakes	100 X 50	Amorphous pitted chunks	None	43
RASE43	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol / Chloroform	0.2	20	37	80	100	16	Fine yellow particulate with yellow flakes	100 X 50	Amorphous pitted chunks with needles, tablets & microsphere	None	62
RASE44	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol / Chloroform	0.2	20	50	80	100	38	Fine yellow particulate with yellow flakes	50 x 50, 10 x 0.5, 10 x 5 & 5 x 5	Amorphous pitted chunks with needles, tablets & microsphere	23.3	78
RASE46	1:1 Ethanol / Chloroform	0.1	PVP (10k)	0.5	1:1 Ethanol / Chloroform	0.2	20	50	80	100	26	Fine yellow particulate with yellow flakes	250 X 200	Amorphous pitted chunks	None	51
RASE48	1:1 Ethanol / Chloroform	0.1	PVP (10k)	0.5	1:1 Ethanol / Chloroform	0.2	20	37	80	100	13	Fine yellow particulate	100 x 100	Amorphous pitted chunks	NA	17
RASE69	1:1 Ethanol / Chloroform	0.1	PVP (10k)	0.5	1:1 Ethanol / Chloroform	0.2	20	50	80	100	10	Fine yellow particulate	100 x 100	Amorphous pitted chunks	None	20
RASE70	1:1 Ethanol / Chloroform	0.1	PVP (10k)	0.5	1:1 Ethanol / Chloroform	0.2	20	37	80	100	8	Fine yellow particulate with yellow flakes	200 x150	Amorphous pitted chunks	None	16
RASE71	1:1 Ethanol / Chloroform	1.1	PVP (10k)	0.2	1:1 Ethanol / Chloroform	0.2	20	50	80	100	72	Fine pale yellow particulate	50 x 50, 10 x 0.5, 3 x 2, 1 x 1	Amorphous pitted chunks with needles, tablets & microspheres	62.3	86
RASE72	1:1 Ethanol / Chloroform	1.1	PVP (10k)	0.2	1:1 Ethanol DCM 1:1	0.2	20	37	80	100	44	Fine pale yellow particulate	50 x 50, 10 x 0.5, 6 x 2, 2 x 1	Amorphous pitted chunks with needles, tablets & microsphere	62.3	81
RASE73	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol DCM 1:1	0.2	20	50	80	100	43	Fine pale yellow particulate	30 x 30, 5 x 0.2, 2 x 1, 0.5 x 0.5	Amorphous pitted chunks with needles, tablets & microsphere	23.3	67
RASE74	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol / Chloroform	0.2	20	37	80	100	13	Fine yellowish white particulate	50 x 50, 5 x 0.2, 10 x 10	Amorphous pitted chunks with needles, tablets & microspheres	37.2	74
RASE75	1:1 Ethanol / Chloroform	0.25	PVP (10k)	0.25	1:1 Ethanol / Chloroform	0.2	20	60	80	100	30	Fine yellow particulate	20 x 5, 5 x 0.5, 4 x 2, 1 x 1	Amorphous chunks with needles, tablets & microsphere	29.1	76
LSDA57	1:1 Ethanol / Chloroform	0.15	EC (7cps)	0.5	Ethanol DCM 1:1	0.2	20	37	80	100	11	Yellow powder	ND	ND	None	10
LSDA58	Ethanol	0.168	EC (7cps)	0.5	Ethanol	0.2	20	50	80	100	67	Yellow powder	ND	ND	None	12
LSDA59	Ethanol	0.170	EC (7cps)	0.5	Ethanol	0.3	20	34	100	100	17	Yellow powder	ND	ND	None	20
LSDA60	Ethanol	0.5	EC (7cps)	0.5	Ethanol	0.2	20	34	80	100	ND	Yellow powder	ND	ND	None	34
LSDA61	Ethanol	1.317	EC (7cps)	0.5	Ethanol	0.2	12	34	80	100	10	Yellow powder	ND	ND	None	13
LSDA63	Ethanol	0.339	EC (7cps)	0.5	Ethanol	0.1	15	50	80	100	89	Fine off-white powder	ND	ND	68	85
LSDA64	Ethanol	1.315	EC (7cps)	0.5	Ethanol	0.1	15	50	80	100	67	Fine white powder	ND	ND	37	50
LSDA65	Ethanol	1.0	EC (7cps)	0.5	Ethanol	0.1	15	50	80	100	89	Fine off-white powder	ND	ND	51	70
LSDA66	Ethanol	0.341	EC (7cps)	0.5	Ethanol	0.1	15	50	80	100	4	Fine white powder	ND	ND	21	42

NA - Not applicable.   ND - Not determined

A two-component nozzle was used in all experiments

Ketoprofen Result Table 6

Experiment	Drug Conc. (%w/v)	Polymer	Polymer Conc'n (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH - J/g)	% Drug in Product by UV (Wt%)
RASG1	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	47	Fine white particulate	<0.1 x 0.1	Amorphous aggregate	None	8
RASG2	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	42	Off-white particulate	0.2 x 0.3	Amorphous	0.1	39
RASG3	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	200	40	Fine white particulate	0.2 x 0.2	Amorphous aggregate	None	11
RASG4	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	200	45	Fine white particulate	0.2 x 0.2	Amorphous aggregate	None	10
RASG5	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	12	37	80	200	38	Fine white particulate	0.2 x 0.2	Amorphous aggregate	None	6
RASG6	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	100	200	42	Fine white particulate	0.1 x 0.1	Amorphous aggregate	None	4
RASG7	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	500	38	Fine white particulate	0.2 x 0.2	Amorphous aggregate	None	8
RASG8	5	NA	0	Ethanol	0.2	15	50	100	200	0	No product	NA	NA	NA	NA
RASG9	5	NA	0	DCM	0.2	15	37	80	200	0	No product	NA	NA	NA	NA
RASG10	5	NA	0	Acetone	0.2	15	37	80	200	0	No product	NA	NA	NA	NA
RASG11	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	39	Fine white particulate	0.3 x 0.3	Amorphous aggregate	None	20
RASG12	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	100	47	Fine white particulate	0.1 x 0.1	Amorphous aggregate	None	12
RASG13	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	100	45	Fine white particulate	0.3 x 0.3	Amorphous aggregate	None	22

NA - Not applicable,   ND - Not determined

All experiments used a two component nozzle

Ketoprofen Result Table 7

Experiment	Drug Conc. (%w/v)	Polymer	Polymer Conc'n (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks (ΔH - J/g)	% Drug in Product by UV (Wt%)
RASG14	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
RASG15	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	10	White cobs	ND	ND	ND	NA
LSDA22	0.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	100	31	Fine white powder	NA	Aggregates	None	22
LSDA23	0.167	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	45	Fine white powder	NA	Aggregates	None	7
LSDA24	0.25	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	39	Fine white powder	NA	Aggregates	None	11
LSDA25	1.0	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	7	Fine white powder	NA	Aggregates	None	25
LSDA26	1.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	ND	ND	Aggregates	1	ND
LSDA27	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
LSDA28	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	0	No product	NA	NA	NA	NA
LSDA29	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	3	Fine white powder	ND	ND	None	49
LSDA30	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	2	Fine white powder	ND	ND	None	52
LSDA36	4.5	HPMC	0.5	Ethanol / DCM (1:1)	0.05	10 N	35	80	200	1	Fine white powder	NA	ND	83	84
LSDA39	2.25	HPMC	0.25	Ethanol / DCM (1:1)	0.05	20 N	50	80	200	0	No product	NA	NA	NA	NA

NA - Not applicable.   ND - Not determined

All experiments used a two component nozzle

N - In these two experiments, nitrogen was substituted for CO2 (flows are in l/min measured at ambient conditions)

Paracetamol Result Table 8

Experiment	Drug Conc. (%w/v)	Drug Solvent	Polymer	Polymer Conc. (%w/v)	Polymer Solvent	Solution Flow Rate (ml/min)	CO2 flow (ml/min)	Temp (°C)	Pressure (bar)	Nozzle np diameter (µm)	Yield (%)	Comments	Morphology by SEM	DSC Peaks (ΔH-J/g)	% Drug in Product by UV (Wt%)
RASF27	0.17	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.1	20	50	120	580	69	Fine powder	10µm diameter irregular chunks, some spheres, some chunks	None	20
RASF30	0.17	Ethanol / DCM (1:1)	HPMC 15cps	0.50	Ethanol / DCM (1:1)	0.1	20	50	120	none	33	Fine powder	spheres, some chunks	None	4
RASF31	0.17	Ethanol / DCM (1:1)	HPMC 15cps	0.50	Ethanol / DCM (1:1)	0.1	20	37	80	none	63	Fine powder	spheres, some chunks	None	19
RASF32	0.50	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.1	20	37	80	580	60	Fine particles produced with some hard lumps	100µm needles & spheres	83.0	ND
RASF34	0.50	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.1	2.5	37	80	580	ND	Particulates with exudate on nozzle	3µm irregular spheres	None	ND
RASF38	0.17	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.1	20	50	120	200	57	Fine powder	10µm irregular chunks	None	17
RASF40	0.17	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.1	10	50	120	200	62	Fine powder	200nm spheres	None	29
RASF43	0.17	Ethanol / DCM (1:1)	HPMC 6cps	0.50	Ethanol / DCM (1:1)	0.1	20	50	120	200	60	Fine powder (large pressure fluctuations)	web like spheres	0	17
RASF96 (RS)	0.1	Ethanol / DCM (1:1)	EC 7cps	0.50	Methanol	0.2	20	34	80	100	65	Fine powder	ND	64	48.5
RASF97 (RS)	0.17	Ethanol / DCM (1:1)	EC 7cps	0.50	Methanol	0.2	20	34	80	100	66	Fine powder	ND	None	21
RASF98 (RS)	0.25	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	100	48	Fine powder	ND	0.2	28
RASF99 (RS)	1.00	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	100	74	Fine powder	ND	105	72
RASF103 (RS)	2.00	Ethanol / DCM (1:1)	HPMC 3cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	100	76	Fine powder	ND	125.5	82
RASF104 (RS)	0.21	Ethanol / DCM (1:1)	EC 7cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	100	ND	Fine powder	ND	158	34
RASF105 (RS)	0.09	Ethanol / DCM (1:1)	EC 7cps	0.50	Ethanol / DCM (1:1)	0.2	20	34	80	50	50	Fine powder	ND	164	12
LSDA35	0.026	Ethanol	EC 10cps	0.5	Ethanol	0.1	20	37	100	200	46	Fine white powder	ND	3	0
LSDA37	0.026	Ethanol / DCM (1:1)	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	120	200	44	Fine white powder	ND	None	2
LSDA46	0.317	Ethanol	EC 10cps	0.5	Ethanol	0.1	20	37	100	200	53	Fine white powder	ND	74	19
LSDA47	0.066	Ethanol / DCM (1:1)	HPMC	0.5	Ethanol / DCM (1:1)	0.1	20	50	120	200	64	Fine white powder	ND	None	2
LSDA48	0.079	Ethanol	EC 10cps	0.5	Ethanol	0.1	20	37	100	200	9	Fine white powder	ND	3	1
LSDA51	0.079	Ethanol	EC 7cps	0.5	Ethanol	0.1	20	37	100	200	16	Fine white powder	ND	None	1

NA - Not applicable,　ND - Not determined

All experiments used a two component nozzle

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Theophylline Result Table 9

Experiment	Drug Conc (%w/v)	Polymer	Polymer Conc (%w/v)	Solvent	Solution Flow Rate (ml/min)	CO_2 Flow Rate (ml/min)	Temp (°C)	Pressure (bar g)	Nozzle tip diameter (µm)	Yield (%)	Product Description	Size (µm, by SEM)	Morphology (by SEM)	DSC Peaks °C (ΔH J/g)	% Drug in Product by UV (W/w%)
RASH1	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	60	Fine white particulate	<0.1 x 0.1	Amorphous aggregate	None	3
RASH2	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	77	Fine white particulate	20 x 20 & 0.1 x 0.1	Amorphous aggregate / tubular	None	20
RASH3	0.17	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	200	77	Fine white particulate	0.1 x 0.1	Amorphous aggregate	None	5
RASH4	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	78	Fine white particulate, some cobs	<0.1 x 0.1 / 20 x 5 / 10 x 1	Amorphous aggregate / platy / acicular	44.5	38
RASH5	0.5	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	85	Fine white particulate, some cobs	<0.1 x 0.1 / 50 x 30 / 3 x 0.1	Amorphous aggregate / platy / acicular	76.2	46
RASH6	0.5	EC 7cps	0.5	Ethanol	0.2	20	37	80	200	13	Fine white particulate	3 x 3	Amorphous aggregate	None	9
RASH7	0.5	EC 7cps	0.5	Ethanol	0.1	20	37	80	200	30	Fine white particulate	3 x 3	Amorphous aggregate	None	5
RASH8	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	37	80	200	69	Fine white particulate, some cobs	0.1 x 0.1 / 20 x 5 / 5 x 0.5	Amorphous aggregate / platy / acicular	(1.1)	21
RASH9	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	74	Fine white particulate, some cobs	0.5 x 0.5 / 20 x 10 / 20 x 1	Amorphous aggregate / platy / acicular	41.3	50
RASH10	0.17	EC 7cps	0.5	Ethanol	0.1	20	50	80	200	41	Fine white particulate	2 x 2 / 70 x 50	Amorphous aggregate / platy	None	28
RASH11	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	34	80	100	47	Fine white particulate	1 x 1 / 2 x 6	Amorphous aggregate / platy	30.3	24
RASH12	0.5	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	78	Fine white particulate	2 x 10	Amorphous aggregate / platy	35.2	48
RASH13	0.17	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	43	Fine white particulate	2 x 2 / 6 x 2	Amorphous aggregate / platy	ND	17
RASH14	0.25	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	49	Fine white particulate	2 x 2 / 8 x 2	Amorphous aggregate / platy	None	27
RASH15	1.0	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	92	Fine white particulate	ND	ND	77.3	67
LSDA41	0.33	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	37	80	500	44	Fine white powder	ND	ND	None	33
LSDA44	0.056	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	6	Fine white powder	ND	ND	None	7
LSDA45	0.056	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	33	Fine white powder	ND	ND	None	2
LSDA52	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	ND	ND	ND	ND	None	17
LSDA53	0.125	EC 7cps	0.5	Ethanol / DCM (1:1)	0.2	20	50	80	200	76	Fine white powder	ND	ND	16.0	20
LSDA55	0.172	EC 7cps	0.5	Ethanol / DCM (1:1)	0.3	20	50	80	100	58	Fine white powder	ND	ND	7.9	26
LSDA56	1.515	HPMC 3cps	0.5	Ethanol / DCM (1:1)	0.1	20	50	80	200	14	Fine white powder	ND	ND	83.7	71

All experiments used a two component nozzle   N.A. - Not applicable.   ND - Not determined

Table 11 - Compound (I) and HPC

Run No.	Solvent	Soln. Conc. (w/v)	D:P (%Drug HPLC)	CO₂ Flow (ml/min)	Soln. Flow (ml/min)	P (bar)	T (°C)	ΔP (bar)	Nozzle Size (mm)	Yield (%)	Particle Size (S) (um)	SEM Morphology / Description	Comments
1	1:1 v/v DCM/EtOH	4.5	89:11	18.0	0.2	90	65	300	0.1	73	16.2 (A)	Clusters of rounded particles < 2um	Small nozzle tip causing large pressure build up
2	1:1 v/v DCM/EtOH	4.5	89:11	18.0	0.2	90	52	300	0.1	72	3.3 (A)	Clusters of rounded particles < 2um and needles < 5um	New 0.1mm tip. Blockages again causing processing problems.
3	1:1 v/v DCM/EtOH	3.5	86:14 (86.7)	18.0	0.2	90	60	280	0.1	70	7.2 (A)	Clusters of rounded particles < 2um. Some needles.	Large pressure build up
4	1:1 v/v DCM/EtOH	3.5	86:14 (78.6)	18.0	0.2	90	70	250	0.2	69	18.7 (A)	Clusters of rounded particles < 2um. Some needles.	Larger nozzle tip does not reduce pressure build up. Higher temp.
5	1:1 v/v DCM/EtOH	0.5	0:100	18.0	0.2	90	70	30	0.2	4	.	.	HPC only using same conditions. A tiny amount of lumps produced
6	1:1 v/v DCM/EtOH	3.0	100:0	18.0	0.2	90	70	300	0.2	47	2.8	Clusters of rounded particles < 2um	Drug only at higher temperature conditions.
7	1:1 v/v DCM/EtOH	1.0	50:50 (43.8)	18.0	0.2	90	70	15	0.2	24	.	Clusters/agglomerates of flake like particles < 2um	Reduced nozzle blockages with higher polymer content.
8	1:1 v/v DCM/EtOH	0.7	30:70 (26.7)	18.0	0.2	90	70	10	0.2	40	.	Agglomerated flakes/plates	Lower nozzle blockages. Particles are more agglomerated
9	1:1 v/v DCM/EtOH	1.0	50:50	18.0	0.2	90	70	10	0.2	53	.	Clusters/agglomerates of flake like particles < 2um	Repeat of run 7
10	35:65 v/v DCM/EtOH	1.0	100:0	20.0	0.2	90	67	120	0.2	72	2.6	Clusters of rounded particles < 2um	Large nozzle blockages. Solvent modified to increase saturation
11	35:65 v/v DCM/EtOH	1.0	85:15	20.0	0.2	90	70	110	0.2	72	22.1	Small particles < 2 um, highly agglomerated.	Sample very agglomerated, hence large particle size results
12	35:65 v/v DCM/EtOH	1.0	85:15	20.0	0.1	90	70	200	0.2	73	3.8	Clusters of rounded/plate like particles < 2um	Large nozzle blockages. Lower soln flow has reduced particle size
13	1:1 v/v DCM/EtOH	3.5	89:11	20.0	0.2	90	70	150	0.2	97	10.8	Agglomerated rounded/plate like particles < 2um	High concentration for greater throughput. High yield
14	35:65 v/v DCM/EtOH	1.0	85:15 (79.0)	20.0	0.1	90	70	150	0.2	95	3.8	Clusters of rounded/plate like particles < 2um	Repeat of run 12
15	35:65 v/v DCM/EtOH	1.0	70:30	20.0	0.2	90	70	45	0.2	84	17.7	Agglomerated plate like particles < 3um, some small needles	Reduced nozzle blockages with higher HPC content.
16	35:65 v/v DCM/EtOH	1.0	100:0	20.0	0.1	90	70	150	0.2	95	2.5	Agglomerated rounded particles < 2um. No agglomeration.	Pure drug sample to be used as a control for dissolution.
17	35:65 v/v DCM/EtOH	1.0	70:30 (64.5)	20.0	0.1	90	70	60	0.2	96	13.1	Agglomerated plate like particles < 2um, numerous small needles	Particles size smaller than in run 15. Reduced solution flow?

Table 12 - Compound (I) and HPC

Run No.	Solvent	Soln. Conc. (w/v)	D:P (%Drug HPLC)	CO₂ Flow (ml/min)	Soln. Flow (ml/min)	P (bar)	T (°C)	ΔP (bar)	Nozzle Size (mm)	Yield (%)	Particle Size (S) (um)	SEM Morphology / Description	Comments
18	35:65 v/v DCM/EtOH	1.0	50:50	20.0	0.1	90	70	12	0.2	73	-		CO₂ ran out mid run leaving wet material.
19	25:75 v/v DCM/EtOH	1.0	50:50 (43.6)	20.0	0.1	90	70	40	0.2	88	28.4	Agglomerated/fused plate like particles	Solvent modified to achieve maximum saturation.
20	20:80 v/v DCM/EtOH	1.0	50:50	20.0	0.1	90	70	30	0.2	-	18.0	Agglomerated/fused plate like particles	Drug solution crashed out mid run. Run abandoned
21	25:75 v/v DCM/EtOH	1.0	50:50 (33.7)	20.0	0.1	90	70	45	0.2	74	20.7	Agglomerated/fused plate like particles	500 ml vessel used to stop material from plugging the nozzle region.
22	20:80 v/v DCM/EtOH	1.0	20:80 (17.9)	20.0	0.1	90	70	12	0.2	27	-	Fused strings of large, > 10 um, rounded, particles	500ml vessel. Very low yield.
23	35:65 v/v DCM/EtOH	1.0	95:5	20.0	0.1	90	70	50	0.2	90	2.8	Clusters of small rounded / plate like particles < 2 um	Addition of 5% HPC may improve dissolution further. Small particles
24	35:65 v/v DCM/EtOH	1.0	85:15	20.0	0.2	130	60	25	0.2	81	15.3	Larger angular particles. Some agglomeration	New P + T conditions reduce ΔP but particle morphology changes

Table 13 - Compound (I) and P-237

Run No.	Solvent	Soln. Conc. (w/v)	D:P (%Drug HPLC)	CO2 Flow (ml/min)	Soln. Flow (ml/min)	P (bar)	T (°C)	ΔP (bar)	Nozzle Size (mm)	Yield (%)	Particle Size (S) (um)	SEM Morphology / Description	Comments
25	DCM	1.0	0:100	18.0	0.1	100	35	-	0.2	-	-		Poloxamer did not precipitate under these conditions.
26	DCM	2.5	70:30 (70.9)	18.0	0.1	100	35	200	0.2	36	14.8	Non-uniform plates and angular particles up to 30 um in size	Severe nozzle blockages. Low yield.
27	DCM	1.75	100:0	18.0	0.1	100	35	35	0.75	62	6.4	Non-uniform plates and angular particles up to 10 um in size	Large nozzle tip to reduce nozzle blocking. Concentration reduced.
28	DCM	1.75	100:0	18.0	0.2	100	35	80	0.75	58	6.1	Non-uniform plates and angular particles up to 10 um in size	Increase solution flow to reduce nozzle blockages.
29	DCM	1.75	100:0	18.0	0.2	100	35	50	-	67	11.3	Large non-uniform chunks up to 20 um in size	No nozzle tip.
30	DCM	2.0	100:0	18.0	0.2	100	70	100	0.2	82	5.2	Clusters of small rounded particles < 2 um	Temperature too high to process poloxamer.
31	DCM	1.0	100:0	18.0	0.1	90	35	65	0.2	75	2.4	Clusters of small rounded particles < 2 um	Reduced T + P, solution conc. and flow rate to get smaller particles
32	DCM	1.0	70:30 (70.1)	18.0	0.1	75	35	45	0.2	82	19.0	Clusters of small plates < 6 um	Introduction of poloxamer changes morphology and particle size.
33	DCM	1.0	50:50 (46.6)	18.0	0.1	75	35	45	0.2	59	-	Agglomerated large plates	Very agglomerated sample.
34	DCM	1.0	20:80	18.0	0.1	75	35	40	0.2	4	-	Agglomerated poloxamer plates	Particles are difficult to precipitate at higher poloxamer contents.
35	DCM	1.0	70:30 (74.7)	18.0	0.2	75	35	40	0.2	27	-	Clusters of plates up to 20 um	Solution flow increased to get higher throughput. Yield reduced.
36	DCM	1.0	85:15 (85.0)	18.0	0.1	75	35	150	0.2	85	11.3	Clusters of small plates < 8 um	Particles appear clustered rather than agglomerated together.
37	DCM	3.0	100:0	18.0	0.2	90	68	350	0.2	75	4.5		Run abandoned midway due to extreme nozzle blockages.
38	DCM	2.0	100:0	18.0	0.15	75	35	150	0.2	92	2.0	Well defined rounded particles < 2 um. No agglomeration	Repeat of run 31 but throughput increased.
39	DCM	2.0	100:0 (95.8)	18.0	0.15	75	35	250	0.2	87	2.1	Well defined rounded particles < 2 um. No agglomeration	Repeat of run 38 to produce a larger batch.
40	DCM	2.0	70:30 (71.3)	18.0	0.15	75	35	250	0.2	95	20.9	Agglomerated plates up to 10 um in size	Wide size distribution. Particle size increase with more poloxamer.
41	DCM	2.0	70:30 (70.7)	18.0	0.15	75	35	170	0.2	95	21.7	Agglomerated plates up to 10 um in size	Material added to run 40 material.
42	DCM	2.0	50:50 (53.7)	18.0	0.15	75	35	100	0.2	77	32.4	Agglomerated plates up to 20 um in size	Larger particles with increase in poloxamer.
43	DCM	2.0	85:15 (86.2)	18.0	0.15	75	35	170	0.2	96	12.3	Agglomerated plates up to 10 um in size	Particle size reduced with lower poloxamer content.

Table 16 - Compound (II) and HPC

Run No.	Solvent	Soln.Conc. (w/v)	Drug:Polymer (Polym. Type)	CO2 Flow (ml/min)	Soln. Flow (ml/min)	Pressure (bar)	Temp (°C)	ΔP (bar)	Nozzle Size (mm)	Yield (%)	Particle Size VMD (um)	SEM Description/Morphology	Comments
1	35:65 v/v DCM/EtOH	1.0	100:0	20	0.1	90	70	200	0.2	74	4.0	Small discrete rounded/granular particles	Fine powder, phase-split conditions (similar to Compound (I))
2	35:65 v/v DCM/MeOH	1.0	100:0	20	0.1	90	70	110	0.2	66	5.5	Slightly aggregated plate-like/rounded particles	MeOH does not appear to help
3	35:65 v/v DCM/EtOH	1.0	100:0	20	0.2	120	60	140	0.2	78	4.5	Slightly larger rounded/granular particles	More angular particles produced with homogenous conditions
4	35:65 v/v DCM/EtOH	1.0	100:0	20	0.2	150	50	200	0.2	64	6.6	Small irregular chunks	Chunk like particles with higher density CO₂
5	35:65 v/v DCM/EtOH	1.0	100:0	20	0.1	150	50	250	0.2	59	8.5	Irregular chunks up to 25um	Problem with BPR during run may have caused larger particles
6	35:65 v/v DCM/EtOH	1.0	85:15 (HPC)	20	0.1	120	60	60	0.2	81	10.3	Dual morphology. Small < 3um and larger acicular particles	Reduced ΔP. Polymer and drug appear to crystallise separately
7	35:65 v/v DCM/EtOH	1.0	85:15 (HPC)	20	0.1	90	70	150	0.2	81	4.6	Clusters of rounded/granular particles	Some fused particles. Sample appears to be a co-precipitate
8	35:65 v/v DCM/EtOH	1.0	85:15 (Low Mw HPC)	20	0.1	90	70	150	0.2	82	4.6	Clusters of rounded/granular particles	Some fused particles. Sample appears to be a co-precipitate
9	35:65 v/v DCM/EtOH	1.0	85:15 (Low Mw HPC)	20	0.1	120	60	70	0.2	85	11.0	Dual morphology. Small < 3 um and larger acicular particles	Reduced ΔP. Polymer and drug appear to crystallise separately
10	Acetone	1.75	15:85 (HPC)	20	0.1	120	60	5	0.2				(50 ml vessel). Stringy polymer mass on nozzle tip
11	Acetone	1.75	15:85 (HPC)	20	0.1	120	60	30	0.1	46		Small primary particles < 4 um heavily aggregated/fused. True co-precipitate	(500 ml vessel). Coarse white powder covering entire vessel
12	61:39 v/v Acetone/Cyclohexane	1.2	15:85 (HPC)	20	0.1	120	60	20	0.1	34		Small primary particles < 5 um heavily aggregated/fused. True co-precipitate	(500 ml vessel). Coarse white powder covering entire vessel. Poor yield
13	Acetone	2.0	20:80 (HPC)	20	0.1	90	70	10	0.1	61	36.5	Small primary particles < 5 um heavily aggregated/fused. True co-precipitate	(500 ml vessel). Coarse white powder covering entire vessel

Table 17 – Compound (II) and HPC (contd)

Run No.	Solvent	Soln.Conc. (w/v)	Drug:Polymer (Polym. Type)	CO2 Flow (ml/min)	Soln. Flow (ml/min)	Pressure (bar)	Temp (°C)	ΔP (bar)	Nozzle Size (mm)	Yield (%)	Particle Size VMD (um)	SEM Description/Morphology	Comments
14	Acetone	2.1	30:70 (Low Mw HPC)	20	0.1	150	50	>200?	0.1	37	-	Small primary particles < 5 um heavily aggregated/fused. True co-precipitate	(500 ml vessel). Coarse white powder covering entire vessel. Problem with run (ΔP?)
15	Acetone	2.1	30:70 (Low Mw HPC)	20	0.1	120	60	20	0.2	80	-	-	(50 ml vessel). Stringy polymer mass on nozzle tip
16	Acetone	2.0	25:75 (HPC)	200	1.0	120	60	5	0.2	60	37.9	Small primary particles < 5 um heavily aggregated/fused. True co-precipitate	Pilot Plant. Coarse/fibrous powder covering vessel walls
17	Acetone	2.0	25:75 (HPC)	200	1.0	120	60	5	0.2	62	12.0	Small primary particles < 5 um heavily aggregated/fused. True co-precipitate	Pilot Plant. Coarse/fibrous powder covering vessel walls
18	Acetone	2.0	30:70 (HPC)	200	1.0	120	60	15	0.2	62	47.1	Dual morphology. Small particles < 4 um and thin wafer like plates.	Pilot Plant. Coarse/fibrous powder covering vessel walls
19	35:65 v/v DCM/EtOH	1.0	90:10 (HPC)	200	1.0	90	50	60	0.2	71	7.9	Dual morphology. Small particles < 2 um but mostly thin wafer like plates.	Pilot Plant. Light, fluffy powder covering whole vessel
20	Acetone	2.0	50:50 (HPC)	200	1.0	120	60	20	0.2	66	33.7	Small primary particles < 3 um heavily aggregated/fused. Appears to be co-precipitate	Pilot Plant. Coarse/fibrous powder covering vessel walls
21	20:55 v/v Acetone/Cyclohexane	1.3	20:80 (P237)	200	1.0	75	35	5	0.2	<10	-	-	Pilot Plant. Thin white film coating walls.
22	Acetone	2.0	50:50 (P237)	200	1.0	80	35	30	0.2	20	-	Agglomerated/fused irregular shaped chunks	Pilot Plant. Thin white powder film coating walls.
23	Acetone	2.0	70:30 (HPC)	200	1.0	120	60	60	0.2	50	13.4	Small primary particles < 3 um heavily aggregated/fused.	Pilot Plant. Light, fluffy powder covering whole vessel
24	35:65 v/v DCM/EtOH	1.0	90:10 (HPC)	200	1.0	90	52	45	0.2	65	6.7	Dual morphology. Small particles < 2 um but mostly thin wafer like plates.	Pilot Plant. Light, fluffy powder covering whole vessel
25	Acetone	2.0	10:90 (HPC)	200	1.0	120	60	5	0.2	63	> 100	Small primary particles < 3 um very heavily aggregated/fused.	Pilot Plant. Coarse/fibrous powder covering vessel walls

References

1   Ford, J.L., (1986) The Current Status of Solid Dispersions. *Pharm. Acta Helv*
61(3), 69-88.

5

2   Yoshioka M., Hancock, B.C. and Zografi, G., (1995) Inhibition of Indomethacin
Crystallisation in Poly(vinylpyrrolidone) Coprecipitates. *J. Pharm. Sci.* 84(8), 983-986.

3   Yoshioka, M., Hancock, B. C., Zografi, G. (1995) Crystallization of
10   Indomethacin from the Amorphous State below and above its Glass Transition
Temperature :- *J. Pharm. Sci.* 83, 1700-1705.

4   Byrn, S. R., Pfeiffer, R. R. and Stowell, J. G. (1999) Solid-State Chemistry of
Drugs, Second Edition SSCI Inc., West Lafayette, Indiana, USA, 249-258.

15

5   Serajuddin, A. T. M. (1999) Solid Dispersion of Poorly Water-Soluble Drugs:
Early Promises, Subsequent Problems and Recent Breakthroughs. *J. Pharm. Sci.* 88(10),
1058-1066.

20   6   Matsumoto, T. and Zografi, G. (1999) Physical Properties of Solid Molecular
Dispersions of Indomethacin with Poly(vinylpyrrolidone) and Poly(vinylpyrrolidone-co-
vinylacetate) in Relation to Indomethacin Crystallisation, *Pharm. Res.* 16(11) 1722-1728.

7   Brocchini, S., Synthetic Polymers for Drug Delivery Applications, *World*
25   *Markets Series "Business Briefing", Pharma Tech, Drug Delivery Supplement*, May
2000, 216-221.

8   Sakellariou, P., and Rowe, R.C., (1995) Interactions in Cellulose Derivative Films
for Oral Drug Delivery. *Pro. Polym. Sci.*, 20, 889-942.

30

9   Hancock, B.C., York, P. and Rowe, R.C. (1997) The Use of Solubility
Parameters in Pharmaceutical Dosage Form Design. *Int. J. Pharm.* 148, 1-21.

10   Romero S., Reillo A., Escalera B. and Bustamente P., The Behaviour of
Paracetamol in Mixtures of Amphiprotic and Amphiprotic-Aprotic Solvents.
Relationship of Solubility Curves to Specific and Nonspecific Interactions 1996, *Chem.*
Pharm. Bull. 44(5), 1061-1064.

11   Subrahmanyam C. V. S., Sreenivasa Reddy M., Venkata Rao J. and Gundu Rao
P., Irregular Solution Behaviour of Paracetamol in Binary Solvents, 1992, *Int. J. Phar.*
78 (1992) 17-24.

12   Barra J., Lescure F., Doelker E. and Bustamente P., The Expanded Hansen
Approach to Solubility Parameters. Paracetamol and Citric Acid in Individual Solvents,
1997, *J. Pharm. Pharmacol.* 49 644-651.

Claims

1   A coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, wherein the amorphous phase active substance is stable, with respect to its crystalline form(s) for at least three months after its preparation when stored at between 0 and 10°C, provided that when the active substance is indomethacin, the polymer is not poly vinyl pyrrolidone.

2   A coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, wherein the amorphous phase active substance is stable, with respect to its crystalline form(s) for at least six months after its preparation when stored at between 0 and 10°C.

3   A coformulation according to claim 1 or claim 2, wherein the amorphous phase active substance is stable for at least twenty four months after its preparation, when stored at between 0 and 10°C.

4   A coformulation according to claim 1, claim 2 or claim 3, wherein the amorphous phase active substance is stable for the specified storage period, when stored at 25°C.

5   A coformulation according to any one of the preceding claims, wherein the active substance comprises a pharmaceutically active substance.

6   A coformulation according to claim 5, wherein the active substance is selected from the group consisting of paracetamol, ketoprofen, indomethacin, carbamazepine, theophylline and ascorbic acid.

7   A coformulation according to claim 5, wherein the active substance is a COX-2 selective inhibitor.

53

8   A coformulation according to claim 7, wherein the COX-2 selective inhibitor is a
diarylheterocycle.

5   9   A coformulation according to claim 7, wherein the COX-2 selective inhibitor is
selected from the group consisting of (Z)-3-[1-(4-bromophenyl)-1-(4-
methylsulfonylphenyl)methylene] dihydrofuran-2-one, (Z)-3-[1-(4-chlorophenyl)-1-(4-
methylsulfonylphenyl)methylene] dihydrofuran-2-one, 4-[5-(4-methylphenyl)-3-
(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-[4-(methylsulfonyl)phenyl]-3-
10   phenyl-2(5H)-furanone and the compound of Formula (III):

(III)
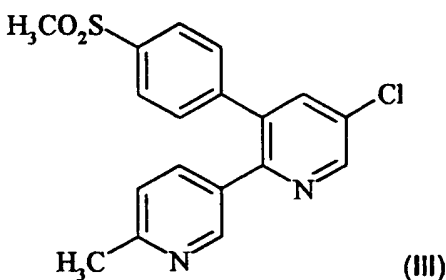
10   A coformulation of (i) an active substance selected from the group consisting of
15   paracetamol, ketoprofen, indomethacin, carbamazepine, theophylline and ascorbic acid
and (ii) an oligomeric or polymeric material, in which between 80 and 100% of the active
substance is present in an amorphous as opposed to crystalline form, and in which the
active substance represents at least 10% of the coformulation, provided that when the
active substance is indomethacin or theophylline, the oligomeric or polymeric material is
20   not poly vinyl pyrrolidone.

11   A coformulation according to any one of the preceding claims, wherein the
oligomeric or polymeric material is selected from the group consisting of cellulosic
materials (including cellulose derivatives), vinyl polymers, poly lactic or glycolic acids
25   (including lactide/glycolide copolymers), and mixtures thereof.

12   A coformulation according to any one of the preceding claims, wherein the active substance is a polar substance and the oligomeric or polymeric material is hydrophobic.

5   13   A coformulation according to any one of the preceding claims, wherein 100% of the active substance is present in an amorphous as opposed to crystalline form.

14   A coformulation according to any one of the preceding claims, wherein the active substance represents at least 20% of the coformulation.

10

15   A coformulation according to any one of the preceding claims, comprising an intimate single-phase mixture of the active substance and the oligomeric or polymeric material, from which the dissolution rate of the active substance in an aqueous medium is no higher for the first 30 minutes than it is subsequently.

15

16   A coformulation according to claim 15, wherein the dissolution rate of the active substance in an aqueous medium is no higher for the first 60 minutes than it is subsequently.

20   17   A coformulation of paracetamol and an oligomeric or polymeric material, in which between 80 and 100% of the paracetamol is present in an amorphous as opposed to crystalline form, and in which the paracetamol represents at least 1% of the coformulation.

25   18   A coformulation according to claim 17 wherein 100% of the paracetamol is present in an amorphous form.

19   A coformulation according to claim 17 or claim 18, wherein the paracetamol represents at least 25% of the coformulation.

30

20   A coformulation according to any one of claims 17 to 19, wherein the amorphous phase paracetamol is stable, with respect to its crystalline form(s) for at least three months after its preparation, when stored at between 0 and 10°C.

5   21   A coformulation according to any one of the preceding claims, which has been prepared by a SEDS™ process.

22   A coformulation of an active substance and an oligomeric or polymeric material, according to any one of claims 1, 2, 10 or 17, the coformulation being substantially as herein described with reference to the accompanying illustrative drawings.

10

23   A pharmaceutical composition containing a coformulation according to any one of the preceding claims.

15   24   A method for preparing a coformulation according to any one of claims 1 to 22, which method involves the use of a SEDS™ process.

25   Use of a SEDS™ process to prepare a coformulation of an active substance and an oligomeric or polymeric material, in which between 80 and 100% of the active substance is present in an amorphous as opposed to crystalline form, and in which the active substance represents at least 10% of the coformulation.

20

26   A method for preparing a coformulation of an active substance and an oligomeric or polymeric material, using an anti-solvent-induced particle formation process, wherein, under the operating conditions used, the active substance is soluble in the chosen "anti-solvent" but the oligomeric or polymeric material is not.

25

27   A method according to claim 26, wherein the particle formation process is a SEDS™ process.

30

28   A method according to claim 26 or claim 27, wherein the anti-solvent is supercritical carbon dioxide.

29   A method according to any one of claims 26 to 28, wherein the active substance is ketoprofen.

30   A method according to any one of claims 26 to 29, wherein the oligomeric or polymeric material is hydroxypropyl methyl cellulose.

31   A method for preparing a coformulation of an active substance and an oligomeric or polymeric material, the method being substantially as herein described with reference to the accompanying illustrative drawings.

Fig.1.

Fig.2.

Fig.3.

Fig.4.

Fig.5.

Fig.6.

Fig.7.

% Release

100 90 80 70 60 50 40 30 20 10 0

00:00:00 00:14:24 00:28:48 00:43:12 00:57:36 01:12:00 01:26:24 01:40:48 01:55:12 02:09:36
Time elapsed (h:m:s)

→ Physical mix (X=20%)   → RASH14 (X=27%)   → RASH6 (X=9%)
→ RASH7 (X=5%)

Fig.8.

Legend:
- Physical Mix (X=20%)
- RASE33 (X=38%)
- Physical Mix (X=20%)
- RASE31 (X=22%)
- Physical Mix (X=20%)
- RASE18 (X=15%)
- RASE40 (X=67%)

X-axis: Time elapsed (h:m:s) — 00:00:00, 00:07:12, 00:14:24, 00:21:36, 00:28:48, 00:36:00, 00:43:12, 00:50:24, 00:57:36, 01:04:48

Y-axis: % Release — 0, 20, 40, 60, 80, 100, 120

Fig.9.

Fig.10.

Fig.11.

Fig.12.

Fig.13.

Fig.14.

Fig.15.

Fig.16.

Fig.17.

Fig.18.

Fig.19.

Fig.20.

X1	152.833 °C
X2	164.500 °C
Peak	161.551 °C
Area	443.511 mJ
ΔH	105.023 J/g
Height	30.729 mW

Fig.21.

X1   118.066 °C
X2   154.066 °C
Peak   139.023 °C
Area   71.937 mJ
ΔH   25.312 J/g
Height 1.488 mW

Fig.22.

Temperature (°C)

(Heat from 25.00°C to 175.00°C at 10.00°C/min)

Heat Flow Endo Up (mW)

Fig.23.

Temperature (°C)
(Heat from 25.00°C to 300.00°C at 10.00°C/min)

Heat Flow Endo Up (mW)

Fig.24.

Heat Flow Endo Up (mW)

Temperature(°C)

(Heat from 25.00°C to 200.00°C at 20.00°C/min)

Fig.25.

Fig.26.

Fig.27.

Fig.28.

Fig.29.

Fig.30.

Fig.31.